VACCINES AND SERA
IN MILITARY & CIVILIAN PRACTICE

A. GEOFFREY SHERA (Hon. Capt. R.A.M.C.)

With an Introduction by
SIR CLIFFORD ALLBUTT, K.C.B., M.D., F.R.S.

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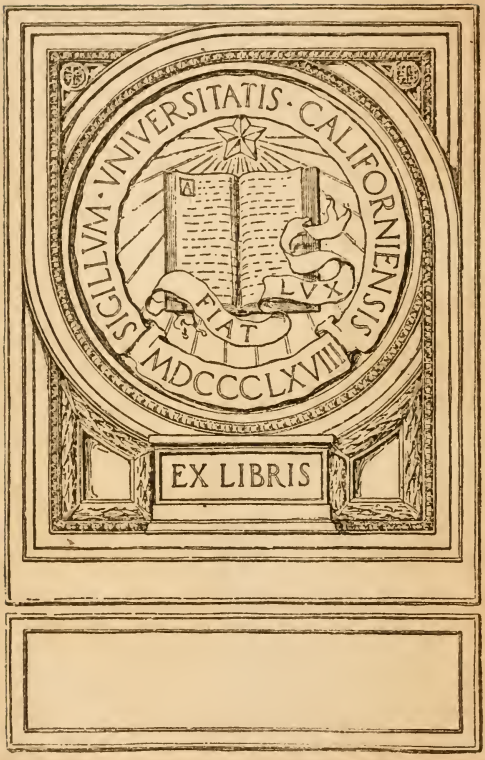
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VACCINES AND SERA

THEIR CLINICAL VALUE IN MILITARY AND CIVILIAN PRACTICE

PUBLISHED BY THE JOINT COMMITTEE OF
HENRY FROWDE AND HODDER & STOUGHTON
AT THE OXFORD PRESS WAREHOUSE
FALCON SQUARE, LONDON, E.C.1

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BY

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WITH AN INTRODUCTION

BY

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LONDON

HENRY FROWDE — HODDER & STOUGHTON

OXFORD UNIVERSITY PRESS — WARWICK SQUARE, E.C.

1918

PRINTED IN GREAT BRITAIN
BY HAZELL, WATSON AND VINEY, LD.,
LONDON AND AYLESBURY.

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ACKNOWLEDGMENTS

I THINK it will generally be conceded by Cambridge students and others who have enjoyed the privilege of working under Sir Clifford Allbutt that their apprenticeship attained a cumulative value with the efflux of time. I would even go so far as to say that, thanks to his charm of manner, incomparable style and admirable exposition, there are very few to whom the Profession would listen more readily than to him. Sir Clifford has set forth the purpose of this little volume with infinitely greater weight and power than I could ever have hoped to do, and I take this opportunity of thanking him for doing me so great an honour. The publication of this book would have lacked much of its value, in fact it would not have occurred, but for the kind permission of my Commanding Officer Surgeon Lieutenant-Colonel Sir W. R. Crooke-Lawless, C.B., who at all times has facilitated my work as far as in his power lay. My thanks are likewise due to the British Red Cross Society for placing apparatus and assistance at my disposal.

In respect of certain technical facilities, I have much pleasure in taking this opportunity of also

thanking Sir Frederick Taylor, late President of the Royal College of Physicians.

I shall not miss this chance of referring to my colleague, Major H. S. Souttar, R.A.M.C., Surgeon-in-Chief to this hospital, in order to thank him for many things, more especially for the benefit of his wide experience in the treatment of developed tetanus and also other matters; the same remark applies to the Senior Physician, Major A. de W. Snowden, R.A.M.C., whose valuable and far-sighted co-operation in relation to the vaccine treatment of chest cases especially has given me very great encouragement. To Captain L. E. C. Norbury, R.A.M.C., I am indebted for permission to introduce the vaccine treatment of the chronic traumatic sinus into the wards of this hospital, the results of which have, so far, been highly effectual. As regards Ophthalmic cases, my thanks are similarly tendered to Captain Hudson and Captain R. Campbell, R.A.M.C. Dr. C. F. Marshall has given me the benefit of a rich experience in many dermatological cases, and, working conjointly, we have secured a very high percentage of successes. I owe Dr. Marshall a particular debt of gratitude for his help in proof-correction and other matter ancillary. I offer my warmest thanks for the encouragement and kindly assistance which Surgeon Lieutenant-Colonel G. S. Robinson, Scots Guards R.P., afforded me in his late capacity of Officer Commanding the Central Military Hospital, Eastbourne, in 1915 and 1916, when, in spite of considerable difficulties, this work

was initiated. Neither have I forgotten the kindness of Major W. G. Willoughby, R.A.M.C. (T), in allowing me the temporary use of the Municipal Laboratory at Eastbourne in 1915.

Captain G. W. Davis, R.A.M.C., late Chief Surgeon at Eastbourne, also Dr. Merry, were, from the first, enthusiasts in regard to the vaccine treatment of the chronic traumatic sinus, and I bear the warmest feelings of gratitude towards them, for it was through their prevision that this work was able to be so successfully applied. To those other doctors of the Eastbourne and Hastings hospitals with whom I worked, the same thanks are tendered, and especially to Dr. Henry L. Ewens, Senior Physician at Eastbourne, to Surgeon Graeme Anderson, R.N., and to Mr. J. Herbert Ball, Dental Surgeon to the Admiralty Air Stations, and formerly to the Central Military Hospital, Eastbourne. Thanks to Dr. P. N. Panton, of the London Hospital, I have been able to avail myself of certain resources of his laboratory, and for similar facilities my thanks are due to Major D. Embleton, R.A.M.C., of the Royal Victoria Hospital, Netley, and also to Captain J. R. Dickson, R.A.M.C., of the Kitchener Hospital, Brighton, and to Dr. T. S. P. Strangeways.

For the most valuable help on matters in connection with this book I beg to thank my old teacher Dr. H. Batty Shaw, Colonel C. Thackray Parsons, R.A.M.C., Dr. Johns (of Harrogate), and Mr. M. S. Mayou, the last especially concerning certain influenzal conditions in relation to the eyeball.

To my own laboratory assistants, particularly to Private W. Soward, R.A.M.C., and Mr. Stanley Woodward (British Red Cross), my thanks are due almost last but by no means least. Finally, I beg to thank the Publishers for their invaluable help and courteous co-operation.

A. Geoffrey Shera.

British Red Cross Hospital,
Netley.
March 30th, 1918.

INTRODUCTION

My friend and former pupil, Dr. Shera, has asked me to write a short introductory chapter to his book; he is good enough to say that I might thus do something more to bring together the bacteriologist and the medical practitioner. It is true that just now such an end is much to be desired, for a phase of eager anticipation of victory over disease by serum and vaccine has given place to a negative phase of disappointment. Not long ago a distinguished surgeon said to me that so much had he been disappointed not only by the failure of the curative vaccines—curative as contrasted with preventive—but also in some instances by their apparently ill effects, that he had determined to retire from any consultation in which vaccine treatment should be proposed. But, if I may judge of my brethren by myself, I should say that we are fairly sure that in vaccination great possibilities lie hidden; that if time after time its services are ineffectual, or even equivocal; or again, if beneficent, yet rather by psychical than somatic influences, still, just when perhaps we are least sanguine, a few successes appear so decisive for good as to lead us

back to the conviction that if we have often failed with this potent instrument—potent for evil as for good—it is because we are as yet far from understanding the use of the weapon ; if some of our blows take effect, others beat the air, and some indeed do damage to our own side. Dr. Shera (p. 85) alludes to the marvellous success now and then of polyvalent vaccines in puerperal cases, good and even brilliant successes which have happened occasionally to most of us, but which we have found ourselves unable to repeat at will. Howbeit, meanwhile it is our duty not to boycott all vaccines and serums, but patiently to work out the laws of specific attraction and immunity ; herein not forgetting the venerable example of Galen who, in his treatise on the Natural Faculties, recognised the marvellous discrimination of the several bodily organs each of which selects from the blood what is precisely akin to itself and rejects the rest.

The ancients had a fine imagination of infinite extension, but no notion of the infinity of the little ; a conception which is becoming clearer to us as we learn of the filterable virus, and, infinitely less than this, the ideal systems of the molecule and atom. And it would seem that one of the conditions on which are balanced the good and harm of vaccines is this very intimate and intense specificity. We are learning this from two opposite directions—from the study of immunity and from that of the natural history of microbes. Whereas once when we had attached a species of microbe to a certain disease we

were satisfied, we are now learning that, as in typhoid fever and cerebro-spinal fever, in pneumonia and its congeners, and in other diseases, we are dealing not with one kind or variety only, but perhaps with three or four; each requiring its own antidote, and refusing to yield an inch to antidotes which are effectual for others with but a shadow of difference from them. Not only so, but again in respect of any one variety, we may have to deal with an endotoxin, or with an exotoxin, or with both together; and so need in the several cases a vaccine, or a serum, or again a combination of the two. For a lack, it may be, of discrimination of these inflexible properties we may fail to use a legitimate instrument aright, or may even use it to our own harm. For instance, the endotoxic chronic gonorrhœa must be "hunted out with a vaccine," the exotoxic diphtheritic angina with a serum, plague with a combination of both weapons. Then, again, there are tides of virulence almost amounting to differences of kind; or, conversely, a microbe adapts itself to the antibodies of its host, so that a vaccine from a new strain of the microbe must be brought in, or, in another sense, as in the case of carriers, the host becomes tolerant of its parasite. Besides, as Dr. Shera points out, microbes from different localities often present variations of quality which find their results in deviations of effects. Furthermore, from such researches as those of Professor Adami, and latterly those of Dr. Hort, it may appear that not a few germs have each two distinct phases, one obvious, the other obscure or even

ultra-microscopic; the former overshadowing the latter in such a way as to leave the obscure phase, previous to these researches, undetected: this appears to be the case in typhoid fever, in swine-fever, and in cerebro-spinal meningitis. In polio-myelitis, mumps, smallpox, and other materially transmissible diseases, most probably the obscure phase exists alone. The chief or only toxic element coincides with the obscure or filterable phase, both phases being essentially vital.

Then, again, a multiplicity of *poisons* may be engendered by one type of germ, even three or four different kinds, as in diphtheria, not one of which is toxic till excreted, *i.e.* pure exotoxins.

In respect of B. tetani, Dr. Tulloch's serological tests indicate that of the toxic kind there are three varieties, from only one of which the antitoxin is prepared. Fortunately in this case the antitoxin seems to protect in a high degree against all three, but probably not completely. A still more remarkable instance is proved by Dr. Bull; namely, that although the varieties of Welch's bacillus are many, yet all are subject to one antitoxin. The narrow structural difference between toxicity and innocence is shown by the demonstration that more than one strain of end-sporing B. tetani can be recovered from wound-exudates which are non-toxic.

Once more, in the bacillary dysenteries there are two poisons—one within the germ and one exterior. Now as one of these—that attacking the surface—acts by an exotoxin which is counteracted by a

serum, the other acts by an endotoxin which escapes the serum, and has to be met by a vaccine. I have published also from time to time clinical reports of several modes of pneumonia which seemed to me to indicate differences in the pneumococcus, each variety having its own modification of the symptoms and needing, it may be, its strictly peculiar antidote. Under all such circumstances as these it is difficult to see how commercial vaccines can be told off each to its own disease without confusion, and perhaps disaster. On p. 13 Dr. Shera shows that in certain cases a very mithridatic of vaccines might be required. For these same reasons also the appeal to statistics, which occasionally makes itself heard, must be premature. Until all these varieties, fluctuations, several properties, and sundry external conditions can be understood, measured, and compared, formal statistics will be impracticable. Meanwhile, for the setting out of our ways, we must depend upon a cautious empiricism and trustworthy personal interpretations.

In passing from these general considerations to the particular chapters of Dr. Shera's work, the reader will find many very interesting opinions, most of them founded on an experience evidently rich and well digested. Dr. Shera is disposed to think that when once a bacterial infection has become a septicæmia, vaccines are not only useless, but, by reducing vital resistance, even injurious. For my part I am disposed to demur to too sweeping a statement on this point. For instance, I have

recently had under my care a man, aged about 55, whose illness began with phlebitis in the right leg ; this had hardly subsided when the other leg began ; in both limbs the process was severe and attended throughout with strongly-marked hectic temperatures. These temperatures continued after the local symptoms had diminished or even subsided, so that for a week or two we were in doubt how far the phlebitis might be passing into suppurative modes, or into some other local or metastatic lesion. On examination of the blood, staphylococcus aureus was cultivated ; but I suspected that it might have arisen from some cutaneous contamination. However, as other cultures gave the same results, we vaccinated the patient with his own microbe. He had five vaccinations, beginning with cautious doses. As soon as the stronger vaccinations began to tell, the temperatures were mastered and the patient, after a grievous illness of many weeks, entered into a good convalescence. Dr Shera, in respect of staphylococcus infections, gives a hopeful view of the cure of sycosis and its allied eruptions. In the cure of acne I think it is not well enough known that the eruption upon the face and back of the shoulders is aggravated by infectious dust from the hair, which ought to be continually and scrupulously cleansed, and not allowed to lie on the bare shoulders.

All military surgeons will turn first to the sections on wound infection, and they will find much to interest them ; for instance, as regards gas gangrene

and its prophylaxis. I read with interest also the paragraphs on sequestrum diagnosis; a gunner, wounded in the leg, of whom I hear from time to time, has been repeatedly returned to hospital for operations upon recurrent separations of sequestra.

Moreover, I may refer to the paragraphs on vaccination in delayed resolutions, and in chronic suppuration. In one case of two years' duration, cure by vaccinations was attained in 47 days. Also the increasing control over cystitis, even in paraplegics, is very encouraging both to physicians and surgeons who have to deal with this distressing complication. And in these methods we are finding new arms against the multitude of infections which threaten the eye, and add to the troops of the blind.

A large field is opened out in respect of mixed infections. Recently Dr. West (*Lancet*, March 9th, 1918) has referred to cases of perilous acute bronchitis in which the pneumococcus, associated with other bacteria, such as the influenzal, had played a leading part; and clinical evidence is accumulating to show the perils of mixtures of other virulent agents, as of the influenza bacillus with other allies. And a new danger has appeared in the liberation of organisms into the blood from phagocytes which had contained but not destroyed them; in this liberation antiseptic agents, such as the hypochlorites, by dissolving the phagocytes, may bring about more harm than good. Thus we find once more how minute and persistent and accurate our defensive measures have to be.

One of the most embarrassing problems of public

health has been the purification of carriers: for weeks and months convalescents are secluded by this kind of quarantine from their friends and occupations. It will be a great help to us if by the resources of bacteriology new weapons can be obtained for the earlier release of these expensive suspects.

The doctrines of immunity, as we now have them, make a wonderful subject of contemplation. It seems impossible to suppose that for every past experience the animal body has stored up a series of antidotes, like rows of bottles in a druggist's shop, each charge standing for years or for a lifetime. Is it not rather that the molecular constitution of the several organs concerned undergo modifications, readjustments, so that discords between invading influences and inward constitution are reduced, even to harmony; that on survival of each infection the corresponding structure is tuned to another pitch, or a group of structures harmonised on another key? To take a much simpler instance, we read concerning fighting aeroplanes that a machine-gun may be fired through a propeller revolving at so many times a second, provided that bullets and blades be set at relative velocities so as to miss each other. So in the body, a resetting of the molecules in this part and that as the several infections may fall, may adapt them to receive such alien vibrations without discord. And it would appear that such modifications may be inherited.

The truth is that substances which, for practical

purposes, we divide into food, enzymes, toxins, and poisons respectively, all interact with the elements of the living body in analogous ways; small differences of tuning, of harmony or discord, between these and the molecular systems of the organism may issue in widely-extending effects. Very small discords in these intrinsic interactions may be propagated through the bodily system with accumulating energy. Conversely, poisons generated in certain plants and animals arise, as it were, incidentally, out of normal metabolism; or by conversion of a normal secretion.

CLIFFORD ALLBUTT.

VACCINES AND SERA

SECTION I

VACCINES

CHAPTER I

THE PRESENT POSITION OF SPECIFIC THERAPY

"The Optimist and Pessimist is what you call a stew."
Modern Song.

CANDID criticism seldom does harm. Herein will be found some of this, but peculiar situations require peculiar remedies, and the present situation of specific therapy, by which one means vaccine and serum therapy, is peculiar. All criticism the author indulges in is general, without prejudice or malice, and in good faith, but he feels very keenly the necessity for arousing medical opinion to the urgency of the situation, and on that score pleads the indulgence of all readers.

Speaking broadly, medical opinion is deplorably chaotic concerning the subject of this book; in some

cases it is even hostile to certain lines of treatment which it purposes briefly to describe; in many cases it almost ignores specific therapy. Yet I submit that pathologists, the progeners of vaccine and serum therapy, have only themselves to thank for such a state of affairs. It is truly pathetic that specific therapy, one of the most brilliant and effective lines of research in modern medicine—and one has but to call to mind diphtheria in order to agree—is in parlous danger of being largely and notably discredited. Such is the case, and I repeat solely due to the fault of the pathologists themselves.

What are these faults? I will not mince matters: undue optimism, due to a lack of perspective, incoherency, intolerance of others' views, and commercial exploitation. As an example of undue optimism, one can remember the time when it was actually claimed that vaccines would cure all varieties of septicæmia! And yet to-day there is very great reluctance to employ vaccines in septicæmia, except perhaps in puerperal cases (which are often largely sapræmic). As a matter of fact, vaccines are generally ignored in septicæmia cases. The reaction from unwarranted optimism is inevitable, for it is based upon results. "Damning with faint praise" would perhaps appropriately describe the form it assumes under such circumstances. Perhaps it would not. Secondly, incoherency. Do two pathologists often agree concerning vaccines or sera, say concerning anti-streptococcus serum? In reply to a request for some anti-streptococcus serum, one set of patho-

logists stated that "owing to the unsatisfactory results from this serum its use had been abandoned, but that they were prepared to substitute a sensitized vaccine."

Many clinicians and pathologists believe in anti-streptococcus serum when it is used discriminately, and one feels that it is much more logical to use a serum in advanced toxæmia than it is to use a vaccine which may lower resistance as a serum cannot, or in the less severe cases to combine moderate doses of both. A vaccine is a toxin, a serum contains antibodies, not toxins. It is perhaps irrelevant to remark that the case in point—one of toxic cellulitis —*did* receive the serum and made an excellent recovery. "*Salus populi suprema lex.*"

Another example of intolerance is afforded by the statement on the part of a pathologist to myself that he did not consider that any one should call himself a pathologist, using the term in the broadest sense, until he had been exclusively engaged in the subject for at least ten years. I wholly disagree. Nothing is more fruitful of pathological myopia than to shut oneself off from clinical medicine, and nothing is more productive of such an intolerance from time to time as is seen in relation to the criticism of bacteriological research work by the pure scientist or by others of an opposing school of thought. Such criticism is often too bitter; moreover, our friends the physicians and surgeons are scandalized by it. It makes pathology and pathologists unpopular. Professor Adami (1) alludes

to the harm such intolerant criticism may do in an admirable article.

Sir Clifford Allbutt was eminently right when he described clinical pathology as the physicians' handicraft. If it becomes anything else, it becomes academic. I will go further and say that no bacteriologist can adequately understand his or her subject unless he or she has a very fair knowledge of clinical medicine and keeps that knowledge fresh, and that, in my humble opinion, the value of a medically unqualified bacteriologist (I do not refer to trained assistants) is merely academic and therefore extremely limited. With regard to commercial exploitation, I feel very strongly that nothing is guaranteed to discredit a line of therapeutics requiring highly scientific handling than is commercial exploitation. That there are scientific reasons for this opinion will be shown herein.

Personally, I have little or no faith in most commercial curative vaccines, though with prophylactic types and with sera the case is different. At any rate, there should be a proper and preferably a Government control of all such manufacture. No matter how good the products are, the principle of uncontrolled manufacture endangers the reputation of such a line of therapy as I am about to describe, and has done much harm already by leading to indiscriminate use and abuse of very potent drugs, namely vaccines.

The day is passing when you either believe in specific therapy or you do not. To-day, the ordinary

medical man hardly knows what to believe, and too much care cannot be exercised in forming an opinion of any one line of treatment.

To quote three instances. Vaccines are reputed to cure acne and chronic bacilluria. They seldom do. They do good, but seldom cure. Serum is reputed to cure tetanus: does it? "I know of no statistics which would hold as evidence in a court of law to prove that A.T.S. *cures* tetanus," is what the surgeon-in-chief of a large military hospital tells me. He is not alone in his opinion. The question of its being worth trial is another matter, however.

Here are three criterions for specific therapy:

(1) "Is it logical?"
(2) "Is it scientific?"
(3) "Is it effective?"

Until these three criterions are satisfied in the specific treatment of any disease, *e.g.* septicæmia, pathologists should not state that vaccines and sera afford sovereign remedies for such diseases. This is good enough to gain time, but is it honest enough to gain credit? Until these things are placed in their true perspective, the general practitioner and ordinary Army M.O. will neglect specific therapy, as they have already done, to a deplorable extent in the case of one of the most fertile and valuable lines of treatment, namely, chronic gunshot wounds.

Having seen these things both from the clinical and pathological point of view, and having ap-

proached the subject of vaccines in time past with a positive bias against them, I have attempted to set down both points of view, the merits and demerits of a line of therapy which I believe has a great future, but a future not so bright as it has hitherto been painted.

If this book serves to bring specific therapy into a more rational, and one hopes a more encouraging perspective, the author will have attained his object. The statistics in Section I are entirely drawn from cases he has treated, except in a few instances, which are noted.

Failures are not ignored.

If the reader is able to make practical use of any suggestions herein contained, he will, I feel sure, not have wasted his time. Conviction, after all, only comes of experience. To put the same thing in another way—"An ounce of fact is worth a ton of hearsay."

CHAPTER II

THE PRINCIPLES OF ACTIVE IMMUNIZATION

Vaccines

Three criterions have been suggested for the consideration of specific therapy, which includes vaccines and sera. They are these:

(1) Is specific therapy logical?
(2) Is it scientific?
(3) Is it effective?

First of all let us consider vaccine treatment and the question of its being logical. It is found that when certain proteid substances are injected into the animal body in increasing doses, at intervals, the body acquires, temporarily, the power of dealing with them. For instance, if washed sheep's red cells are injected into a horse in this manner, the serum of the horse acquires the power, under suitable conditions, of dissolving sheep's cells. The exact mechanism of such solution is academic so far as we are concerned, but if one substitutes a killed suspension of bacteria in suitable doses, in the case of cholera, the immunized animal will acquire the

power of actually dissolving those bacteria (Pfeiffer's phenomenon). Washed kidney cells can similarly be dealt with, a cytotolysin being formed which has the power of dissolving renal cells (nephrotoxin), and so one could multiply examples.

Now Wright, to whom we owe the application of vaccine treatment to Man, has defined a vaccine thus :

" Bacterial vaccines are sterilized and enumerated suspensions of bacteria which furnish, when they dissolve in the body, substances which stimulate the healthy tissues to a production of specific bacteriotropic substances (or antibodies) which fasten upon and directly or indirectly contribute to the destruction of the corresponding bacteria."

Allen has given us a graphic description of the theory of the mechanism of vaccine therapy, the aim of which he states is " to exploit the healthy tissues in the interests of the unhealthy." The process is known as Active immunization, and is quite different from the Passive immunity produced by sera, and vaccines are quite different from sera in their mode of operation, and it is to be regretted that medical men frequently confuse the two terms.

I have carefully avoided the academic details of Ehrlich's side-chain theory, very ingenious though it be, but reference must be made to the two rival theories of the bactericidal action of the body. Ehrlich brought forward much evidence to show

that bacteria are killed by the body fluids; on the other hand, Metchnikoff brought forward much evidence to show that certain of the leucocytes (phagocytes) kill off the bacteria unaided by the body fluids. People who support the former view are called "humoralists," and those who support the latter are known as the "cellular theorists."

There is much to be said for both theories. Their full discussion should be sought for in larger works upon immunity, but the point is that the two theories are not essentially divergent, and that we are unwarranted in clinging to one to the exclusion of the other. The question rests largely upon a recognition of the cells which are the most active in producing antibodies, and upon the rôle of the phagocyte. Ehrlich's theory is chemical, Metchnikoff's "vitalistic." A study of physiology leads one to lean rather to the chemical theory and to consider phagocytosis as mere scavenging; nevertheless the question is largely unsettled. If phagocytosis is the chief or only means by which bacteria are destroyed, the opsonic index (G), which is a relative measurement of phagocytosis, should furnish us with a complete picture of the mechanism of immunity. Unfortunately it does not do so, and has been practically discredited. It was nevertheless a most ingenious idea, which we owe to Wright. Enough has been said to show that vaccine therapy does satisfy two out of the three criterions, namely, that it is both logical and scientific to use vaccines therapeutically.

(G) Refer to Glossary.

It now remains to show whether vaccines are effective.

The author proposes to deal with certain diseases in which this line of treatment has been tried, in detail.

Sera will be dealt with later.

The question of the different types of antibodies produced will be dealt with, as they arise, under the individual headings.

CHAPTER III

VACCINES

Technique for Preparing Bacterial Vaccines

A. Ordinary Non-sensitized Vaccines

Bacterial vaccines are made by procuring infected material, by preparing cultures of the bacteria that are to be combated, and by making suspensions of these in normal salt solution, adding a preservative and placing in proper containers.

To procure the Material.—One must procure "the virus, the whole virus, and nothing but the virus," so far as aërobic bacilli are concerned. It is essentially the business of the pathologist to see that effective precautions are taken against contamination.

Pus from an abscess cavity or sinus should only be taken after the surrounding tissues have been sterilized with 2% tincture of iodine or picric acid solution. The "harmless" Staphylococcus albus must not be included when we are dealing with the Staphylococcus aureus.

Nasal secretion may be obtained after cleansing the nasal orifice, and passing a sterile swab through

a speculum and rubbing the surface of the lower turbinates and septum.

The ear should likewise be thoroughly cleansed and a culture made from pus.

As regards **sputum,** the patient should brush the teeth with a sterilized tooth-brush and rinse the mouth with 1 in 100 phenol, and then swallow some boiled water and expectorate coughed-up material into a wide-mouthed sterile bottle.

Lung-puncture is a dangerous process and is best avoided.

Urine, of course, should be withdrawn under strict aseptic conditions.

Blood specimens are taken with a sterile syringe from a prominent vein at the elbow after sterilizing the skin and bandaging above the elbow with a Bier's bandage in order to induce congestion.

Preparing the Cultures.—This is not always easy. Some bacteria require special media; for instance, the influenza bacillus and the gonococcus and sometimes the pneumococcus.

First of all, stain a direct smear by Gram's method. In this way one should not miss any important bacterial infective agent.

Cultures may then be made upon solid media, but personally the author prefers to inoculate the infective material into broth tubes and subculture upon agar plates. This method will not do for the influenza bacillus, or for the gonococcus, which should be grown upon hæmoglobin-serum-agar.

In making a vaccine for all cases except these, one

agar plate is sufficient. Four to six tubes of serum-agar are needed for the special cases mentioned.

When the organisms are exposed to equal conditions of growth as closely resembling the body conditions as possible, the author has avoided separating them, *e.g.*, in the case of a bacilluria containing Bacillus coli and Staphylococcus aureus, and has made a mixed vaccine, enumerating the two (or more constituents) respectively, and he has found that the proportions in which they grow are practically identical with those in which it is common to give them ; for instance, the proportion of B. coli communis and B. coli communior are not separated out before making the bacterial emulsion. I have used this method in vaccines prepared from sputa and gunshot-wound pus, and I believe that hereby one generally hits off the correct relative amount of antibody required more accurately than by the laborious method of separation. It is advisable to employ the first subculture, but this is not always done. The "United States Medical Corps" use a very ancient culture of typhoid bacilli for its vaccine.

The Preparation of the Emulsion.—Observing strict asepsis, freshly sterilized saline solution is poured over the culture and then the growth is very lightly removed from the agar by a platinum loop, previously flamed. The suspension is now filtered through sterilized filter paper in a funnel into a sterile test-tube, except in the case of such fine growths as the streptococcus, where it is better to

transfer the emulsion direct to another tube which is drawn out and sealed off in the flame and thoroughly shaken, mechanically or by hand.

The advantage of filtering the culture is that it removes all clumps and pieces of agar which may accidentally have got into the emulsion.

Before sterilizing, funnels are made ready with the filter-paper clipped in the metal clips. Filtration is fairly rapid, and one does not often get contamination by " air-bacillus " (B. subtilis) (G) through exposure, especially if the whole apparatus is covered with a bell-jar.

The emulsion must in all cases be homogeneous. There is evidence to show that bacteria grown on media containing peptone may produce toxic substances capable of giving rise to anaphylactic phenomena. Serum, moreover, if washed off, may do the same. Therefore it is as well to centrifugalize all suspensions until the supernatant fluid gives a negative biuret reaction (G). This is seldom done, but at any rate one should centrifugalize once and test the supernatant fluid with Fehling's solution. If it turns pink, then further washing should be undertaken.

Counting the Emulsion.—Wright's method was to mix equal parts of whole blood and emulsion and, knowing the number of red cells per cubic millimetre, to deduce by proportion the number of bacteria per cubic centimetre.

This method is open to certain technical errors. Sources of error are introduced thus :

(1) In mixing the emulsion and blood. Some may be lost, *e.g.* through clinging to the side of the pipette.
(2) The film is inevitably unequally distributed.
(3) A margin of error occurs in counting the bacteria.
(4) A margin of error occurs in counting the red cells.
(5) A margin of error occurs in the proportion sum.

Total, five sources of error.

Now if a dilute solution of methylene blue in filtered sterile distilled water is used instead, and by employing a sterilized Thoma or Watson pipette to dilute the emulsion 1 in 200, a direct count is made, as for red blood cells, and the sources of error are few.

Errors Nos. 2, 3, and 5 may occur, but to a lesser degree. Wherefore this method is much more accurate.

If one cannot afford to lose time by sterilizing the pipette, the emulsion may be thoroughly agitated in a sealed tube, and a portion then removed and counted as a sample.

Dilution according to the strength of vaccine required can then be undertaken.

Rougher methods of enumeration appear to work well if the dose is based on clinical results, but are quite unscientific and may lead to slovenly work. The author has seen laboratory assistants trained in these methods put their fingers over the ends

of the tubes containing suspensions and pieces of media and pour out the suspensions, keeping back the larger pieces of agar with the finger. It is well that the clinician should make sure of the methods employed where his vaccines are made!

Rougher methods are based on average estimates of the number of germs per slope grown in, say, 18 hours, or upon the number of germs per loopful (Kolle's method), or by sedimentation (Hopkins).

The method of dilution the author employs is to count the suspension, say, of Staphylococcus aureus, in freshly sterilized normal saline (0·85%). Suppose it works out at 6,400 millions per c.c., and that one requires a vaccine of 1,000 millions per c.c., 5 c.c. are measured out accurately after shaking well, and they are made *up to* $\frac{6400}{1000}$ parts—6·4 parts, *i.e.*, *up to* 32 c.c., with normal saline solution; 0·1 c.c. phenol per c.c. of vaccine is added as a *preservative*.

The author uses bottles of 20 c.c. capacity. One of these previously plugged and sterilized is taken and the diluted vaccine poured in. Rubber caps which have been soaked for some time in phenol 1 in 50 are carefully fitted by means of sterile forceps and wired on with fine iron wire. Then the cap and neck are dipped in the following:

Collodion flexile . . .	2 parts
2% Tinct. Iodi	1 part

and left to dry.

Sterilization in a water bath at 56° C.–60° C. for

45–60 minutes is performed, and by means of a sterile syringe and needle the cap is pierced and at least three agar slopes are inoculated and incubated for 24 hours. Serum agar is, perhaps, safer to use, as it is more sensitive, or the vaccine itself can be incubated first, if time permits. All vaccines which are not sterile are rejected. A second heating means impaired potency, and in the case of contamination with air-bacillus this is useless, as this germ forms resistant spores.

With ordinary care, failures will be few and far between. Enclosing vaccines in separate ampoules is troublesome and usually unnecessary, but can be done if required. All ampoules should be immediately tested for sterility by taking a few loopfuls of each on to serum agar before sealing.

Vaccines should be kept in the dark and preferably in a refrigerator.

B. Sensitized Vaccines

Kakehi (1) has shown by immunizing experiments upon animals with sensitized and non-sensitized vaccines that the toxicity of the former is less than that of the latter. A sensitized vaccine is a vaccine treated with its corresponding immune serum for 6–12 hours at room temperature. The idea is to hasten the process of immunization by performing the first stage *in vitro*. Living bacteria have been used thus sensitized. It was Metchnikoff and Besredka who first practised sensitization.

Theoretically, the idea is brilliant. Practically, there is not much advantage. Possibly it may be worth further trial in septicæmia, despite repeated failures in most cases. There is to my mind a fallacy connected with its application in the latter cases. How can one obtain an immune serum for preparing the patient's autogenous vaccine? Manifestly there is not time to treat the patient's organisms with the immune serum of the same *species* of germ, and to treat it with that of a different germ is, to my mind, mere waste of time, since every germ produces absolutely specific antibodies. Linking up your patient's organisms to another serum is, moreover, likely to diminish the potency of your vaccine to the detriment of your patient, even if you grant that vaccines do good in septicæmia, which is extremely doubtful.

CHAPTER IV

THE ADMINISTRATION OF BACTERIAL VACCINES

Syringes.—A 2 c.c. syringe boiled in a beaker half filled with methylated spirit, together with needle and forceps, for 3–5 minutes, is all that is required.

When sterile, put together, well paint the top of the vaccine bottle with iodine, or break the ampoule and aspirate what you require, expelling air before injection.

Site of Injection.—The upper arm beneath the deltoid muscle or the forearm in the firm part below the elbow anteriorly are good places. Otherwise the scapular or pectoral muscles do very well. Sterilize the skin with iodine. Place the vaccine fairly deeply and withdraw the plunger of your syringe to ensure that a blood vessel has not been entered; withdraw the needle gradually as you inject.

After-effects.—The local effects vary with the dosage and the individual. Thin people are much more prone to reactions than well-covered people. People with acne of any degree are likewise prone to after-effects in the author's experience.

In most cases there is some reddening and soreness after 8–10 hours, remaining thus for 24–48 hours, and succeeded by some itching. In many cases there is practically no discomfort, and *if the dosage is determined by accurate counting of the vaccines, this especially holds good.* Stock vaccines, one finds, are much more prone to give reactions than are autogenous ones.

In the more severe local reactions, *e.g.* after the second dose of army typhoid vaccine, there may be considerable œdema, pain and inflammation of the corresponding lymphatic glands. Hot fomentations will relieve this in a few days. In some cases a somewhat severe local reaction will be followed by an urticarial eruption on the arm, and later by a transient but irritating dermatitis, which I have known affect the arms and legs, axilla, groin, scrotum and abdominal wall. This occasionally may last for some time and is difficult to relieve. It appears to be worse in the female sex. The irritation is extremely trying at night time. I have found that great relief follows the following application:

℞ Sulph. præcip. . . . . grs. xx
Acid. salicyl. . . . . grs. xx
Benzoated lard . . . ad ℥j
M. ft. ung. Ut. p.r.n.

It appears to be due to some proteid toxin, but the author has only met with it in very few cases (four in a large series). In all these there was a somewhat heavy dosage employed; it can, therefore,

surely be avoided by starting with a low dose and working up gradually.

Constitutional Effects Vary.—They are generally absent, but are most marked in *lung* cases, where great care must be taken in limiting dosage. In one case where the M.O. accidentally gave a double dose, a condition resembling pleuro-pneumonia resulted. The patient's life was almost despaired of, but he was quite himself again in ten days. As a rule there is some lassitude, headache and perhaps a pyrexia of 99°–100° F., and an acceleration of the pulse.

Given moderate dosage, I repeat that constitutional symptoms should be absent.

In cases where reactions occur, it is usually the fault of the administrator.

Dosage and intervals will be dealt with under the individual diseases. Wherever possible, the bacteriologist should give his own vaccines.

CHAPTER V

DISEASE GROUP: DISEASES OF THE SKIN

Disease: **Smallpox**

Vaccination

Vaccination in smallpox is limited to prophylaxis.

In 1718, Lady Mary Montagu, the wife of the British Ambassador in Constantinople, noticed the practice amongst the Turks, who performed it in order to preserve the beauty of the young Turkish and Circassian women. She had her own son and daughter inoculated, and introduced the practice into England. Subsequently, Jenner, in 1796, experimentally used cowpox vaccine prophylactically, but met with much opposition.

Smallpox vaccination is the greatest triumph of prophylactic vaccination known.

The **preparation of the vaccine** (1) is interesting and usually absent from most medical books. Female calves from 2–4 months old are taken. They are sometimes tested with tuberculin and always kept under observation for a few days, then clipped and thoroughly cleansed. The belly is completely shaved and prepared as for operation. About 100

small scarifications are now made under strict asepsis. Slight bleeding occurs, which is mopped up. The virus, which is obtained from a human case and preserved on sterile bone "slips," is inoculated on each area. The lesions are allowed to dry. Sterile gauze then covers the lesions. The animals are kept clean, excreta being promptly removed. The animal must not kick itself. Within 48 hours a reaction occurs, and the animal is killed after 6 days. Strict asepsis, as for operation, is observed. The field of papules is cleansed and curetted. After curettage serum exudes. "Slips" are charged with this, and the pulpy exudate is made up thus:

Glycerine	50%
Water	49%
Phenol	1%

The glycerine pulp is left standing 3–4 weeks, as it is always infected with bacteria. At the end of this time these should have undergone dissolution. The pulp is then triturated and put up in capillary tubes.

The vaccine is tested bacteriologically and not put up till sterile. Also it is tested for tetanus and its potency estimated by the type of vesicle it produces.

Here in England the manufacture is largely under Government control. In America, Government inspection invariably occurs, a practice which might well be extended to all commercial drugs in this country.

An autopsy on the calf so as to discover if healthy, is necessary.

Vaccination.—To secure successful vaccination I am firmly convinced that a trace of bleeding *must* occur. The usual site is over the deltoid muscle, and it should never be done on the leg for mechanical reasons. Blowing through the tube with the mouth is unwise and uncleanly. It is said that the stabbing after cross-scarification favours the growth of anaërobes—but this is very doubtful. Immunity certainly runs parallel to the number of scars. Aseptic precautions should be observed throughout. Neglect of these leads to severe reactions.

Phenomena.—In a successful case the sequence of events is as follows :

About the 3rd day—a slight red elevation occurs with burning and itching.

About the 6th–7th day—the umbilicated grey vesicle with areola.

About the 10th day—maximum effect, irritation intense, several small vesicles outside the main one.

About the 12th–21st day—scabbing and return to normal.

In children, after the 5th day, restlessness occurs, followed by pyrexia where "taking" occurs.

The "reaction of immunity" is worth mention. It occurs in folk who have been previously successfully vaccinated, and consists of an areola at the old site of inoculation. It appears at the end of 24 hours

and disappears at the end of the 3rd day from inoculation.

A diminutive vaccine papule which goes away by the end of the first week is known as "vaccinoid."

The eruptions which occasionally follow vaccination are usually of an erythematous or dermatitic nature.

Duration of Immunity.—Seven years is the usual limit, but where smallpox is common, *e.g.* in Serbia, it is advisable to vaccinate yearly or six-monthly. If the subject is immune, it will not "take," so no harm is done.

The risks of vaccination are:

(*a*) Tetanus.
(*b*) Syphilis.

If the vaccine is properly made, these risks do not arise. The protective value of vaccination against smallpox is not called in question by any reasonable person nowadays. If the protection is not complete, a mild degree of disease with no subsequent disfigurement occurs in vaccinated people.

Statistics.—The British Army, particularly the Salonika force, in itself to-day furnishes sufficient evidence for all time as to the efficacy of vaccination for smallpox. Previous to the war, the mortality from smallpox in England was 7·5 times higher (2) than in Germany, which certainly carried out vaccination more thoroughly than we did.

CHAPTER VI

DISEASE GROUP: DISEASES OF THE SKIN (*continued*)

Disease: **Furunculosis or Boils**

Ætiology.—Boils are caused by staphylococci, occasionally by streptococci, and rarely by the Bacillus coli. A consecutive series of 47 cases occurring in the British Red Cross Hospital, Netley, in the summer and autumn of 1917, with one exception, were caused by the Staphylococcus aureus. The diagnosis is clinical, then bacteriological. *Hæmoculture is advisable in severe or relapsing cases*, but ordinarily the skin is sterilized with iodine and the pus transferred by means of a flattened platinum wire previously flamed, to a broth tube, incubated for 8–10 hours and plated out on to agar plates. Occasionally, the streptococcus is found and rarely the Staphylococcus citreus, but often S. albus and S. aureus are found together. Boils following *scabies* almost always contain streptococci with staphylococci of either variety. The same germs appear, as it were, to cling round certain localities such as hospitals. Not only patients, but nurses

and orderlies get infected, and small epidemics do appear to occur. Here are some figures of my own cases :

A series of 16 consecutive cases at the Central Military Hospital, Eastbourne.

Infecting Organisms.	Cases.
Staphylococcus albus alone	3
,, albus and aureus together .	5
,, aureus alone	1
,, aureus and a streptococcus .	4
,, albus and a streptococcus .	3
Cases in which Staphylococcus albus was present	11
Cases where S. albus was absent . . .	5

On the other hand, here are 47 consecutive cases at the British Red Cross Hospital, Netley.

Infecting Organisms.	Cases.
Staphylococcus aureus alone	46
Bacillus coli alone	1

A consideration of other cases, such as sycosis, acneiform cases, gunshot wounds, cystitis and even respiratory cases, show that the Staphylococcus aureus at Netley invades a very large number of patients. It has the compensation, however, of being exceedingly amenable to vaccine treatment.

The Toxins of the Staphylococcus.—There are two exotoxins (6) excreted by the staphylococcus, staphylolysin and leucocidin. *In vitro*, a growth on broth which is faintly acid produces staphylolysin in 3–4 days, reaching its maximum in 14 days, and heat at 56° C. destroys the toxin. Staphylolysin

is a hæmolysin (G)—*i.e.* it produces hæmolysis. Boils thus tend to anæmia and iron is indicated therapeutically. Leucocidin is produced under similar conditions, but is distinct, being more easily destroyed by heat. It kills leucocytes, but also can kill ganglionic cells—*i.e.* it is not specific. Phagocytosis is interfered with in the presence of leucocidin, and the giving of yeast in boils is a scientific practice, for it stimulates phagocytosis.

A third thermostable endotoxin (G) (*i.e.* within the cell bodies of the cocci) is present in young cultures which do not contain the other two; by itself it causes local irritation and pyrexia.

The Antitoxins of the Staphylococcus.—These are antistaphylolysin, present naturally in considerable degree in the horse, and antileucocidin. Antistaphylococcus serum can be prepared artificially, and contains antibodies for staphylolysin and leucocidin. Its use is advocated in severe, spreading or metastatic staphylococcal infections where phagocytosis is poor, as determined by a blood-count.

By means of appropriate modifications of the technique of the Wassermann reaction, both staphylolysin and leucocidin and their antibodies can be demonstrated and titrated. In man, the antibodies are naturally present in small quantities.

Anti-staphylococcus serum has not been found to be very successful, no doubt because the third (endotoxin) factor is missing, and also because a large amount of antibody is not produced. Much greater success has attended vaccine treatment,

Nevertheless in severe, toxic cases the serum should be tried.

The Toxins of the Streptococcus pyogenes.—A hæmolysin, a filterable toxin and an endotoxin (*i.e.* contained in the cells themselves) occur. The hæmolysin accounts for the sanguineous exudate met with in streptococcal infection. The filterable toxin (streptolysin) has less toxicity than the endotoxin, which latter accounts for the virulence of this germ. The subject is not fully understood as yet. Sera which will clump (agglutinate) streptococci can be produced by immunizing animals. As a means of diagnosis comparable to the Widal reaction (G), however, agglutination (G) is negligible.

The Antitoxins of the Streptococcus.—Human blood contains a natural antibody for the streptolysin, and streptococcus serum is sometimes of great value. Its effects may be observed in some cases within an hour or two of injection. The temperature may fall and the local condition improve immensely. In boils, however, the serum is scarcely needed except in very severe cases.

The toxins of Bacillus coli are dealt with later.

The Prophylaxis of Boils.—In military practice this becomes a serious problem. Epidemics appear to occur, as also more rarely in civilian practice. They are so common amongst soldiers that the total number of days of incapacity for which they are responsible does reach a very high figure. At the moment I am vaccinating 20–30 cases a week in a military hospital of 1,000 beds, and they are not the

full total of cases extant. One cannot but feel that if each case on entry, or perhaps in France where boils are very common, received a stock prophylactic injection of a local strain, *e.g.* from cases in the same hospital, that many days' incapacity might be prevented. It does not require much imagination to see that the loss of efficiency due to boils in the Army must be totally very great. Many cases develop boils only after entering hospital. This applies to orderlies and nurses who often appear to get infected from dressings, especially on the arms.

Treatment.—Failing prevention, vaccination with autogenous vaccines offers in at least 86% of the cases a cure in a fairly short time. In some cases in a week or two ; in others in a longer time.

Here are some figures concerning the duration of treatment. In all but one case the injections were given every 10 days.

A Series of 36 Consecutive Cases Chosen at Random and Treated by the Author Throughout

	Cases.	Average duration of treatment.
Treated and cured with **autogenous** vaccines only	10	39·7 days (4 or 5 injections)
Minimum time taken in any one case to be cured (*i.e.* no relapse whilst traceable)	—	20 days (3 injections)
Maximum time under same conditions	—	70 days (8 injections)

	Cases.	Average duration of treatment.
Treated and cured with **local stock** vaccines	16	55·1 days (6–7 injections)
Minimum	—	20 days (3 injections)
Maximum	—	110 days (12 injections)
Treated and cured with **autogenous vaccines, after local stock vaccines** had been tried and failed	5	65·4 days (7–8 injections)
Cases sent out before treatment complete	4	
Cases remaining in uncured after prolonged treatment	1	
	36	
Percentage of certain cures		86·1
Percentage of certain failures		2·77
Percentage of doubtful cases		11·13

Now, with regard to the one failure in this series, who is still under treatment (December 1st, 1917). The boils began after signs of intolerance to Salvarsan. This man had a positive Wassermann reaction and tertiary ulcers over the right tibia. I had two cases of boils which did not react to vaccines, in another hospital, both of which had positive Wassermann reactions. It is as well, therefore, in cases of intractable boils to bear syphilis in mind. In two cases of such boils I have found the Spirochæte pallida in these boils. At that time the boils were deeply ulcerated with a sloughy, wash-leather

base and clear-cut edges. Previous to this stage they were typical boils. The general treatment for boils should include the administration of iron and purgatives. A watch must be kept for recurrences. In a military hospital this is difficult, since men usually go out soon after treatment. In such cases as those only taking 20 days to cure, recurrence may occur later. One always asks the patient to write and say if recurrences occur, but no such sequelæ have come to my notice.

The Nature of the Vaccine to be employed.—A study of the figures given on pages 30 and 31 shows that the best results are given by autogenous vaccines (G), the second best by stock (local) vaccines followed by auto-vaccines, and the third best by stock (local) vaccines alone. Commercial vaccines I have tried repeatedly, and the only result has been failure or worse, aggravation. The author remembers the case of a general practitioner who was treating a rather sensitive elderly lady for acne and boils with a commercial vaccine. One morning she came to him as an appalling mixture of rosacea, comedones and indignation. Since when the aforesaid doctor has foresworn all vaccines for all time. It is just this kind of mistake which does harm to the reputation of vaccines.

Clinical and pathological experience all go to show that the staphylococci and streptococci are specific in their dealings to some considerable extent. Whereas a vaccine made from Netley cases will do good to cases occurring in Netley hospital, one made from

London cases is found to be useless. In regard to prophylaxis, the same rule applies I believe, but to a lesser degree.

In a severe case of boils, therefore, no time should be lost in making an auto-vaccine (G). In mild cases stock preparations of local strains may be tried, but mean *a delayed cure* as compared with auto-vaccines.

With Regard to Dosage and Intervals.—A vaccine containing 2,000 millions of staphylococci per c.c. is convenient to work with. On the first day, give 0·1 c.c., on the tenth day 0·2 c.c., and so on. Doses greater than 1 c.c. of this strength are inadvisable.

If the vaccine is mixed, *e.g.* Staphylococcus albus and a streptococcus, the initial dose of streptococcus should be about 20 millions. The vaccine would be made thus:

	Millions per c.c.
Staphylococcus albus . . .	2,000
Streptococcus	200

Initial dose, 0·1 c.c.

Where a mixture of staphylococci occurs, 1,000 millions per c.c. of each is made up.

Bacillus coli rarely occurs in boils. The primary vaccine dose is 100 millions (*e.g.* vaccine 1,000 millions per c.c. Initial dose, 0·1 c.c.–100 millions).

Intervals.—In one's own experience nothing is to be gained by frequent injections; moreover they may do harm. The body deals slowly with the staphylococcus and forms antibody slowly as complement-

deviation (G) tests show. Ten days is a good standard interval, a 5 days' interval has no advantage.

The Neisser-Wechsburg Phenomenon

Experiments with bacteriolytic sera have proved that they only protect against specific infections in certain doses. Neisser and Wechsburg showed this *in vitro*, and it is known as the Neisser-Wechsburg Phenomenon. Excess of serum is as ineffectual in sterilizing the bacteria as is none at all. Wherefore if one gives too much vaccine or gives it too often, which comes to the same thing, our antibody will not be properly correlated to requirements. Leave the body to do its own work in its own time, and all will be well.

Changing the Vaccine.—It is a fact that the infecting germs may become resistant to the antibodies evoked in a long case of vaccine treatment, just as trypanosomes (G) can become atoxyl-resistant (G). Occasionally in cases of boils, the vaccine should be changed and a fresh one made, say every three months in cases lasting so long. This changing is much more necessary in some other infections when chronic, *e.g.* Bacillus coli cystitis, where the organism adapts itself to unfavourable environment more readily.

The Estimation of Effect.—Clinical observation furnishes this. If more exact data are required, complement-deviation tests are useful, as also are bactericidal tests with the whole blood. The opsonic

index formerly was widely used, but its value to-day is questionable.

Reactions.—These phenomena usually indicate overdose. The doses I have indicated are for men. Tolerance to poisons varies with body-weight, and due allowance for this must be made in soldiers of small stature, and in women. (See Section III.)

Slight local reactions occur in about 25% of cases. General reactions are very rare. Nevertheless they must be guarded against, and a purge should always be taken overnight. The local treatment of reactions consists of foments combined with rest. Sedatives are rarely necessary. Boils, for a week or two, *may* become more frequent, but gradually less severe. This is all part of reaction and is a good sign. A vaccine should *not* be stopped if such things occur.

Preserving the Vaccine.—Any noticeable change in the vaccine or its cover should be followed by its immediate despatch to the laboratory where it was made, for testing. No vaccine should be used after three months' storage. Every vaccine should be vigorously shaken before use, as the germs settle at the bottom or in clumps.

In one case, a vaccine was returned to me which had had its cap removed, contrary to express instructions. It was full of "air bacillus." In this condition an injection had actually been given, and the matron of the V.A.D. Hospital indignantly inquired why it had made the patient ill! Fortunately he recovered without any obvious ill-effects.

Sensitized Vaccines.—The rationale of these is to

avoid the first toxic stage of vaccine injection. If a small enough dose is given, they are unnecessary in furunculosis.

Surgical Treatment.—This must never be neglected on any account whatever. If the bacteriologist expects to be fairly treated by the surgeon, he must do the same by the surgeon.

CHAPTER VII

DISEASE GROUP: DISEASES OF THE SKIN (*continued*)

Disease: **Acne**

Ætiology.—There are two essential lesions in acne (G), namely, the comedone, the "black-head" which is the plugged sebaceous gland from which the anaërobic (G) acne bacillus may be grown, and the inflammatory pustule which supervenes and which is caused by a staphylococcus, usually S. albus.

A reference to the ætiology of acne has some bearing on its bacteriology. This disease is commonest in young men from 18–25. In these there appears to be a lack of tone in the skin and its appendages. This atonic condition was shown in one case by the fact that hairs falling on the shoulders would implant themselves upside-down in abnormally open sebaceous ducts and be retained quite firmly. Also the cutaneous circulation is generally very poor in these cases, and in addition to lack of tone in the skin, the central nervous system, which is of the same embryonic parent, the epiblast, is often abnormal. Acne is common in neurasthenics and epileptics for instance, is often associated with

phosphaturia, which in turn is doubtless due to abnormal nervous metabolism. Another factor in cases of acne is due to digestive derangements of metabolism leading to absorption of metabolic toxins, as evidenced by indicanuria (G) coupled with constipation. All these factors lead to diminished bacterial resistance in the skin. They are thus primarily mechanical, *e.g.* abnormally open sebaceous glands, secondarily nutritional, *e.g.* poor circulation, and thirdly toxic, *e.g.* in acne of alcoholic gastritis.

Whether the whole problem is referable to an abnormal central nervous system alone, or to an abnormal epiblast (G) giving rise to an abnormal skin and central nervous system at the same time, cannot easily be proved. At any rate the mechanical factor no doubt indicates easily infected sebaceous glands by omnipresent germs, and poor circulation means ineffective antitoxic resistance, and metabolic toxins indicate further aggravation.

Hence it is scientific to recommend open-air exercise, steaming of the face in acne, together with massage, also gastric therapeutics and nervous tonics. Expression of the plugs of sebum should be carried out.

The staphylococcus is in most cases S. albus, often misnamed "harmless."

The Toxins and Antitoxins.—These are the same as regards the staphylococci as in the last chapter.

The pathological function of the diphtheroid acne bacillus has been questioned by some folk. This germ may be grown anaërobically on oleic acid agar.

It grows anaërobically at the bottom of the plugs of sebum. The advisability of making vaccines from anaërobic bacilli is very questionable. These bacilli are often very resistant to heat, and so by the time they are killed their therapeutic usefulness in vaccines has gone.

Spirochæte Vincentii, the anaërobic rods and spirochætes found commonly in many throats, were once used as a vaccine in a case known to Dr. Strangeways, and led to a fatal general septicæmia. Many anaërobes form spores. As a general rule it is inadvisable to make vaccines from anaërobes. In acne this rule applies also in my opinion. It may account for the comparatively large number of failures to cure one has experienced with this type of case, but personally one finds that other folk, *e.g.* certain American bacteriologists (1), get just as unsatisfactory results when using the acne bacillus. Cases of extreme aggravation following injections for acne may be due to unkilled acne bacilli in the blood introduced with the vaccine.

Using the staphylococcal vaccine alone, one has had a few apparently complete cures, usually much improvement and few if any complete failures.

Here is a recent series of 12 consecutive cases at Netley:

	Cases.	Average duration.
Cases treated with **autogenous** vaccines only.	7	82·5 days (8–9 injections)
Maximum duration of any one case	—	104 days (11–12 injections)

	Cases.	Average duration.
Minimum duration of any one case	—	61 days (6–7 injections)
Cured	1	
Improved markedly	4	
Incomplete	2	
Cases treated with **stock** (**local**) vaccines	4	63 days (6–7 injections)
Maximum duration, etc.	—	75 days (7–8 injections)
Minimum duration, etc.	—	54 days (5–6 injections)
Cured	0	
Improved	2	
Incomplete	0	
No appreciable change	2	
Cases treated with **commercial** vaccines	1	
Made worse (Vaccine then changed)	1	

Brilliant cures within a short time are rare in acne. I can recollect only one. Constitutional causes account for this. Vaccines apparently only play a secondary part in the cure of the ailment.

The Nature of the Vaccine.—Autogenous or local strains are advisable.

Here particularly commercial vaccines may do much harm.

The Dosage and Intervals.—A vaccine of 2,000 millions of staphylococci, 0·1 c.c. of which is given on the first day, 0·2 c.c. on the tenth day, 0·3 c.c. on the twentieth day, and so on up to 1 c.c.; this constitutes a useful standard treatment.

Alteration of Vaccine.—A new vaccine will be necessary at the end of three months.

Estimation of Effect.—This is purely clinical.

Reactions.—Acne subjects are very liable to reactions from small doses. The nearest axillary glands may swell accompanied by local erythema at the site of injection, headache and a pyrexia of one or two degrees.

Sensitized Vaccines.—These may be tried. There is a scientific reason for this, namely, the toxic susceptibility of the acne subject.

Surgery.—Pustules and boils require local surgical treatment occasionally.

Disease: **Sycosis** (G) **(and Impetigo** (G))

Ætiology.—Some writers consider sycosis very intractable. Personally one has found these cases very amenable, except when associated with eczema. The organism is either the Staphylococcus aureus alone or together with S. albus, and rarely the streptococcus.

Orderlies and patients, I am sure, often get it from each other, and the former from handling infected dressings. The variety commonly met with in military hospitals is impetiginous, and as a rule is very amenable to cure.

The toxins and antitoxins have been described. Prophylaxis is only called for where a large number of cases are associated with healthy people, with whom, needless to say, they should not be associated, if possible.

A recent consecutive series of 10 cases of mine show the following results :

	Cases.	Average duration.
1. Cases treated with **autogenous** vaccines only . . .	7	37 days (4–5 injections)
Maximum time for a cure . .	—	50 days (5–6 injections)
Minimum time for a cure . .	—	20 days (3 injections)
Two cases went out of hospital before treatment was completed.		
2. Cases treated with **stock (local)** strains	2	57 days
Maximum time for a cure . .	—	48 days (5 injections)
Minimum time for a cure . .	—	10 days (2 injections)
3. Case treated with **commercial** vaccines . . . . (Treatment changed to treatment with autogenous vaccine)	1	
	10	

In every case the Staphylococcus aureus was present, and in two cases the Staphylococcus albus was evident as well.

It will be seen that in this disease local strains are worth trial. The case cured in 10 days was a mild one.

A change of vaccine is only called for in prolonged cases, which are rare unless associated with eczema. These are dealt with under the heading of eczema.

The dosage and intervals are as before.

The effects are estimated clinically.

Reactions are uncommon. Sensitized vaccines are unnecessary. Surgical treatment consists of the usual local applications, *viz.* fomentations, etc.

Disease : **Eczema**

It is only when this disease becomes one of secondary infection, *e.g.* when it occurs after scabies, as it often does associated with boils, that vaccine treatment is likely to do good. A pyodermia associated with a very recent case of generalized eczema of a very irritative variety, and with the staphylococcus citreus as the secondary infecting agent, cleared up as regards the pyodermia, but left the eczema.

An eczema capitis of the impetiginous variety did well with an autogenous vaccine, as also did a post-scabies eczema associated with boils which disappeared with the boils. In the latter class of case it is most important to get rid of the scabies, since if this is not done the lesions are very intractable. A case of eczema with boils which was very intractable proved subsequently to have a positive Wassermann reaction. The organisms present in these cases are the Staphylococcus albus and aureus together or alone, with or without the Staphylococcus citreus.

The dosage and intervals are the same as before, and sensitized vaccines are not necessary.

Recently, a number of cases have come to my notice of a contagious type. The disease began with irritation of the skin of a pruriginous type. Minute, watery vesicles appeared from which the staphylococcus citreus could be grown.

Excoriation supervened or the vesicles subsided, and on the axillæ, legs, or buttocks an extremely painful infiltrated type of boil appeared. From these boils again Staphylococcus citreus was obtained in pure culture. In one case, a husband developed boils, and a week later his wife also, although previously the wife had had much more severe excoriations on the fingers. Vaccines were made in both these two cases. The result of these was a speedy cure of the boils in one case with an auto-vaccine. The eczema cleared up with sulphur and salicylic acid ointment. In the other, whilst the eczema was similarly cured, the boils took some time to clear up, but eventually both were cured. Both these latter patients were associated with military hospital work, the husband particularly. The author has seen other cases of this pruriginous "vesicular" eczema. Boils followed in each in due course. One other case had timely treatment with the above-mentioned ointment, and did not develop boils. The latter case was not associated with hospital work, whereas the former were. It is possible that this vesicular eczema predisposes to boils by excoriating the skin and so facilitating further and deeper infection.

Disease : **Pyodermia** (G)

This condition is essentially a streptococcal infection. In its pure form there are multiple pustules of the hand, leg or groin, forehead or face, covered with dried blood. In the impure form the streptococcus is associated with a staphylococcus, generally of the aureus variety, but in eczema often the staphylococcus citreus is present. The duration of treatment in the pure form averages about 30 days. The author has used commercial vaccines with little if any success. The initial dose of streptococcus vaccine is 5–20 millions, and is gradually increased. This disease occurs both in military and civilian work, but not to a great extent.

Disease : **Erysipelas**

As American writers (Kolmer, for instance) have pointed out, stock vaccines of the Streptococcus erysipelatis are of no value if of the commercial type. In an apparent epidemic, local strains may be of use, but even autogenous vaccines appear to have little influence on the course of the disease.

Antistreptococcus serum is the scientific drug to use in such a toxic infection, although a sensitized vaccine may be tried in mild cases.

Opinion is divided on this subject.

Ross and Johnson of Toronto in 1908 (2) give two series of 19 cases each, which certainly would lead one invariably to employ vaccines in erysipelas

if they are true of *all* cases. These are their figures :

How treated.	Temperature normal in 24 hours.	Temperature normal in 48 hours.	Average duration of pyrexia in days.
Non-specific . .	3	13	8·9
Specific . . .	9	5	3·1

	Complication.	Average duration of illness in days.
Non-specific . . .	In 6	25·0
Specific	In 1	12·8

One must confess that the above series is very convincing until one reads that the non-specific cases were taken from the year 1907 *and the specific from 1908*. Now any medical man knows that infective diseases (and erysipelas is no exception) are never of the same virulence in any two years.

Wherefore in 1908 probably the authors were dealing with a mild epidemic, and in 1907 with a more severe epidemic. Thus, a possible fallacy becomes apparent, a fallacy which, to my mind, is insuperable. Another factor overlooked is this, the Streptococcus erysipelatis of Toronto is by no means the same organism or likely to have the same virulence as the Streptococcus erysipelatis of London. In the chapter on furunculosis it has been shown how locality accounts for changes in types of the same disease.

On the whole, vaccines in erysipelas are dangerous (except possibly sensitized vaccines, whose value is questionable) and by no means reliable. It is safer and more scientific to use a serum.

Disease: **Other Skin Diseases**

Fistula, sinus, diabetes, gangrene, glanders, lupus, pemphigus vegetans (G), ulcers due to Bacillus Vincentii (G), and mycosis fungoides (G) have all been happy hunting-grounds for vaccine therapy The present-day opinion in all these cases is indeterminate, and until the case for vaccines is proved in these instances they are best left alone, so far as specific therapy is concerned.

CHAPTER VIII

DISEASE GROUP: INFLAMMATION OF CONNECTIVE TISSUE

Disease: **Cellulitis,** including Whitlow, Mastitis, Adenitis, etc.

Ætiology.—The streptococcus is the chief criminal in this respect; the staphylococcus comes next, and occasionally we find the colon bacillus. These cases vary much in severity; from cases with nocturnal delirium to a mild chronic cellulitis.

Usually the toxins are of a severe nature. The occasional appearance of the Bacillus coli in these cases bodes no good to the patient. Septicæmia may supervene in the severe prolonged cases, but fortunately is not common. Cases of Ludwig's angina (G), which come under this head, give rise to a peculiar kind of cellulitis of the neck due to the presence of the streptococcus and staphylococci. Allen drew attention to the fact that in these cases blood-clot sometimes prevents free access of lymph. This condition can be relieved by 60 grain doses of citric acid, three-hourly. He has treated such cases with vaccines. The point concerning a free lymph

exudate is a good one, and citric acid medication in all cases of cellulitis is a good course to pursue.

Bacillus pyocyaneus (G) (blue pus bacillus), often seen in wound infections, may give rise to a cellulitis. This organism is eminently amenable to vaccine therapy (see chapter on chronic gun-shot wounds). Cases of chronic mastitis, though uncommon in military work, are not uncommon in civilian practice. There is great interstitial thickening in many cases. Vaccine therapy often clears these up. Residual thickening in cases of cellulitis is best treated by whirlpool baths followed by massage directly afterwards, and in the case of the limbs by passive movements.

The organisms of cellulitis are hereby tabulated from 15 recent military cases:

Streptococcus alone	5
Staphylococcus aureus alone	5
Streptococci with S. aureus	2
Streptococci, Staphylococcus albus . .	2
Staphylococcus aureus and albus together .	1
	15

It is interesting to note that the Staph. aureus cases were all at Netley, the Staphylococcus albus cases were at Eastbourne, which again exemplifies my remarks concerning the way in which different germs appear for the time being to be indigenous in different localities.

In regard to cures and duration of treatment, and the best type of vaccine to employ, the following figures are useful to some extent:

15 consecutive cases.	Cases.	Average duration of treatment.
Cases treated and cured with **autogenous** vaccines only . . .	9	59·15 days (6–7 injections)
Minimum time for a cure .	—	25 days (3 injections)
Maximum time for a cure .	—	103 days (10–11 injections)
Cases treated with **local stock** strains	2	
One cured in	—	55 days (6 injections)
One died of pneumonia		
Cases treated with **commercial stock** vaccines	4	
One failed to improve and was given an autogenous vaccine and subsequently got well .	—	12 days
Three others		
Minimum time for a cure .	—	10 days
Maximum time for a cure .	—	15 days

The average duration of cases cured with autogenous vaccines is unduly high because one case lasted 103 days and another 92 days. The statistics are small because one has not included gunshot wounds with their sequelæ. These are dealt with in the next chapter. One's own impression is that in mild cases of cellulitis commercial vaccines may do good. This is, I think, the only category one knows where they are of real use, and this is because cellulitis is one of the most favourable fields for vaccine therapy there is, if not the best in material results. The toxins are mainly endotoxins in the case of the bacilli of the coli-typhoid group (B. coli and B. pyocyaneus). Antitoxins to these bacilli are

notoriously abundant and easily evoked, as shown by the high degree of agglutination conferred by anti-typhoid and anti-colon inoculation.

The best vaccine to use is an autogenous vaccine, although very fair results may be obtained by the use of stock vaccines in suitably chosen, *i.e.*, mild cases.

Prophylaxis in one respect is more applicable to suppurating gunshot wounds than to these cases; nevertheless a prophylactic injection before an operation given overnight undoubtedly minimizes the risks of "flares," *i.e.* rises of temperature, rapid pulse and general deterioration after operation.

The dose of such prophylactic injections should be *as for a primary therapeutic dose, e.g.*

	Millions.
Streptococci	20
Bacillus coli	50
Staphylococcus aureus . . .	200

In actual therapy, the dosage and intervals are *as for the individual germs.*

For instance, in a mixed vaccine:

		Millions.
1st dose (1st day)	Streptococci . .	20
	Staphylococcus aureus.	200
	Bacillus coli . .	100
		—— (0·1 c.c.)
2nd dose (10th day)	1 . .	40
	2 . .	400
	3 . .	200
		—— (0·2 c.c.)

			Millions.
3rd dose (20th day)	1	. .	60
	2	. .	600
	3	. .	300
			—— (0·3 c.c.)

and so forth.

In prolonged cases there should be three-monthly changes of vaccines, *i.e.* a new vaccine should be made. This especially applies to bacilli of the coli-typhoid group which rapidly adapt themselves to their new environment. A curious phenomenon will often be noticed in prolonged cases. One organism may die out completely, *e.g.* Bacillus coli, and be replaced by one which was not formerly present, *e.g.* Staphylococcus aureus. This applies also to cases of suppurating gunshot wounds and to cases of chronic bacilluria. In all cases of cellulitis which do not clear up, if near bony structures, *look for sequestra*. The author has been able more than once to diagnose sequestrum by the kind of reaction the patient presents to vaccine therapy. This will be dealt with in the next chapter more fully.

The estimation of effect may be estimated :

(*a*) Clinically { locally. / generally.

(*b*) Bacteriologically, by a rough estimation of the number of organisms in films from the wound stained by 2% watery methylene blue for 3 minutes.

If one cares to do the thing scientifically, one can estimate the titre of agglutination (G) of the patient's serum (Widal test modified) in coli-typhoid group infections, and also the amount of anti-staphylolysin

by the technique described in Kolmer's *Immunity*. Clinical evidence is usually sufficient, however.

Vaccines are a great boon in these cases. The author remembers one old gentleman in a London hospital who, through a whitlow followed by cellulitis, lost the complete use of one arm, and suppurated for two years and had innumerable operations. Since using vaccines in these cases, cures have seldom exceeded three months, and in many cases became effective in a few weeks.

Reactions.—If the dose is properly regulated and not given oftener than once in ten days, these will be absent. Dosage must be regulated to body weight. Thus for a man a full dose, as already indicated, should be given, for a well-developed woman three-quarters of such a dose, and to a small man half to three-quarters of a dose, and to a small woman half a dose.

In the very toxic stages, one surgeon I know suspends the vaccine and uses a stock serum. Sensitized vaccines are perhaps justifiable in very toxic cases, but a small dose is just as safe. Unless septicæmia is superimposed, no fear need be entertained, even in the occasional event of delirium from toxæmia.

Surgery.—Sequestra must be removed. Indolent sinuses must be scraped and all pent-up pus freed. Prophylactic vaccination previous to operation is advisable. X-rays are very useful in these cases to determine the nature of sinuses and the presence of sequestra, and are usually not sufficiently employed

CHAPTER IX

DISEASE GROUP: DISEASES OF THE GENITO-URINARY SYSTEM

Disease: **Cystitis**

Ætiology.—In order to apply vaccine treatment rationally in cystitis, it is essential that a proper understanding of the ætiology of the complaint should be arrived at. It is, for instance, no good vaccinating a man with an enlarged prostate, or calculus, with cystitis until the cause of retention, *i.e.* the enlarged prostate, has been dealt with. Likewise it is useless to vaccinate for cystitis where the cause lies in a continual reinfection from a chronically inflamed appendix adherent to bladder. Yet this is frequently done, and the bacteriologist perchance receives scorn in return for failure. And he is to blame. It is his business to see that his powers are not misapplied at the risk of being accused of selecting only specially favourable cases.

Cystitis may be acute or chronic. The acute cystitis of the young woman who may be what Panton calls "a colon carrier," that is, she has already been mildly infected by reason of certain

anatomical arrangements which favour this, induced by a sudden chill or other factor which lowers bacterial resistance, is very amenable to vaccine treatment. Recently, three injections of an autogenous vaccine brought about a complete cure of an acute and severe case. Polyuria was very marked, especially at night, pus and bacilli were numerous, and the infection was mixed (B. coli and Staphylococcus aureus). There has been no return of trouble since cure (7 months ago). The secondary infection with cocci is not necessarily a late complication.

Another type of acute case is that of the paraplegic soldier who lies out perhaps 24 hours or more, shot in the spine, and is then catheterized under rough-and-ready conditions at the first opportunity, 90% of whom develop cystitis later. Some time ago Mr. Thomson Walker, in a paper (1), dealt admirably with these cases, which are collected at the "Star and Garter" Hospital, Richmond, and recommended vaccines in their treatment, which he has found very useful. Early cystotomy and drainage are also recommended by him as a prophylactic measure. I venture to think, also, that prophylactic stock vaccines are also worthy of trial in such cases, and if successful would be a less radical line of treatment than cystotomy. *The eminent success of prophylactic vaccination in other diseases of the colityphoid group is assuredly a justification for a trial in these cases.*

The exact bacteriological diagnosis of cases of cystitis when they have arisen is very important—

perhaps more so than in any other infection where vaccination is to be used, and for a certain reason. Organisms of the coli-typhoid group have the faculty of adapting themselves to conditions in such a way, as Emery pointed out (2), that they may actually change their type in order to conform to new conditions. For example, a vaccine for B. coli cystitis usually becomes useless after three months, as the organisms have adapted themselves to the antibodies evoked, and progress will hang fire until a fresh auto-vaccine has been made. This fact of specificity accounts for many failures in vaccine treatment, and is a striking condemnation of such things as commercial stock vaccines in these cases. It is, moreover, not sufficiently recognized. Another possible fallacy in these cases is that of mistaking a "colon-carrier" for a case of pathological cystitis. Clinically, the distinction is easy, for a "colon-carrier," as Panton has pointed out, has no symptoms. Colon-carriers are often women who, for anatomical reasons, get easily infected. They are, of course, potentially pathological, and an exciting cause, say a chill, will often convert them into cases of cystitis.

A true bacilluria is an unmistakable phenomenon. Another important point is the presence or absence of pus. If a bacilluria is found accompanied by pus, the infection is urinary (and probably also renal—infective nephritis). If no pus is present, the infection is probably hæmatogenous, *e.g.* from a suppurating gunshot wound. I recollect two cases of severe bacilluria in which the Bacillus pyocyaneus

was the only organism present, which was also, at the time I came across the cases, the only organism present in their chronic suppurating wounds of the leg. Other sources of hæmatogenous infection are the intestine, an inflamed appendix, etc. Adhesions between gut and bladder, or between appendix and bladder, or a chronic salpingitis or perineal abscess, may cause cystitis or pyelonephritis or both. In all these cases the cause must be borne in mind in prescribing vaccines, and if the latter fail these possible causes must again be referred to and excluded if possible, if success is to be reasonably expected.

The organisms of the coli-typhoid group usually present in cystitis are those comprehended by the terms Bacillus coli, Bacillus coli anaërogenes, Bacillus proteus, and Bacillus pyocyaneus, and occasionally B. acidi lactici and B. Friedländer. As secondary invaders, one may find staphylococci (usually the S. aureus), streptococci, diplococci (not pneumococci, but culturally distinct) and diphtheroid bacilli. In suspected cases of hæmatogenous infection, hæmoculture is advisable. Bacillus fæcalis alcaligines may sometimes be recovered in this way, originating from the gut. The Bacillus typhosus or the paratyphoid bacilli may be present in cases of those fevers. Finally, in all *cases of bacilluria and pyuria, the tubercle bacillus must be excluded.* Tuberculous cystitis does not come within the scope of vaccine therapy.

The Toxins and Antitoxins.—Bacillus coli produces a hæmolytic toxin (colilysin) and an endotoxin

on which its pathogenicity mainly depends. The vaccine is somewhat toxic. Bouillon filtrates are practically atoxic. Agglutination, which is a part of the reaction of immunity, is developed slightly after vaccine treatment, but not nearly so markedly as in typhoid inoculation.

Emery (3) has shown that bacteriolytic substances are developed. These appear to be only *temporarily* specific—that is to say, that a vaccine may in time lose its potency owing to the organism becoming antibody resistant, just as trypanosomes may become atoxyl-resistant. This is more marked in this group of bacilli than in any other, but applies to all vaccines in some degree, and its non-recognition accounts for many failures, and its recognition will be the death-blow to commercial *therapeutic* vaccines of this type (not to commercial *prophylactic* vaccines). The above applies to bacilli of the coli-typhoid group.

The Bacillus pyocyaneus in animals, if injected, causes locally, hæmorrhagic œdema and generally septicæmia with nephritis and wasting. The vaccine is potent, judging by one's experience with pure infections in gunshot wounds.

Hagner (4), of Washington, used the Bulgarian bacillus (B. acidi lactici var.) to combat the Bacillus proteus. He claims that symbiosis of these two organisms is impossible, and introduces cultures of the Bulgarian bacillus into the bladder as a therapeutic practice. He claims the elimination of the Bacillus proteus in these cases. This practice re-

minds one of two other suggestions: one was the drinking of diluted pus recommended in a paper which appeared in the *Practitioner* a few years ago, and the other the sowing of wounds with the so-called Reading bacillus recently commended by Lieutenant-Colonel Mayo-Robson (5). These lines of treatment seem to me to possess risks; for instance, in the latter case of introducing the tetanus bacillus alongside the sporing Reading bacillus, which hardly justify their employment. That, however, is a matter of opinion.

Prophylaxis.—In respect of acute paraplegia due to gunshot wounds, a prophylactic injection of a vaccine of a mixed type would be well worth trying, and the practice might well be extended to all paraplegic cases likely to develop cystitis. The initial dose should be 50 million coliform organisms and 100 millions staphylococci, and the secondary dose, 10 days later, 200 millions of the former and 500 millions of the latter.

Statistics.—In a series of nine consecutive cases, seven were confirmed chronic cases before they reached me. Two were acute and one a double infection. Both cleared up within one month, and now (7 months later) are absolutely free from signs or symptoms. Of the other seven, one had an enlarged prostate. The vaccine relieved his frequency and pain, but he still has pus. He will not be cured except by the intervention of a surgeon. Two cases received four injections and returned to duty with no pus and only a few bacilli. Two

gunshot-wound cases lost their symptoms, but retained their bacilluria. One is, I believe, tubercular. A case with old abdominal inflammatory trouble received no benefit. One other case was relieved of symptoms. This case one suspects as being tubercular. Only one case received stock vaccines and did not do well. The minimum duration for any one case was 1 month, with 3 injections; the maximum was 6 months, with 18 injections. This series was rather an unfortunate one, as there were only 2 acute cases, but this was owing to the fact that these were not the commonest type of case at Netley. Definite renal infection occurred in the one acute case and also in two of the others. The only absolute failure was the case treated with stock vaccines.

In chronic cases cure is rare, as Emery has shown, but symptomatic relief can usually be attained. It is most important not to neglect the surgical aspect of these cases.

Dosage and Intervals.—I usually begin with 50–100 millions of coliform organisms and about 100–200 millions or more of staphylococci if present. Suppose the vaccine to contain 500 millions B. coli and 1,500 millions Staphylococcus aureus per c.c. The first dose one would give would be 0·1 c.c., *i.e.* 50 millions and 150 millions. Wait 10 days and give 0·2 c.c., *i.e.* 100 millions and 300 millions, and so on. Every vaccine must be autogenous (and sensitized if preferred), and must be changed every three months.

Reactions I have not found common. Agglutination may be tried if leisure permits, and in all cases not improving once more exclude tubercle and surgical complications.

Hæmoculture may sometimes give a clue as to the origin. In one case one isolated the Bacillus fæcalis alcaligines in this way and traced the origin of a cystitis to the gut. The use of potassium citrate, or, alternatively (in alkaline urines), hexamine and acid sodium phosphate, is a part of treatment not to be omitted.

Disease: Pyelitis and Nephritis

The first may be a sequel to cystitis with an over-distended bladder or to malignant growths in the lower urinary tract. Again, nephritis may be primarily or secondarily streptococcal, possibly primary in the throat, as Saundby (6) suggests. In these latter cases vaccines often do much good. In the former, more caution must be exercised in determining whether or no there is a pure microbial infection and not a malignant growth. Tuberculin is dealt with in a subsequent chapter. It is not recommended.

Disease: Urethritis, Gonorrhœa

Ætiology.—Urethritis of the acute type is almost always gonorrhœal, but the chronic type is not, and the acute type may not be specific. Besides the gonococcus, the following bacilli may be found: Micrococcus catarrhalis, Bacillus proteus, Bacillus

coli, Bacillus influenzæ, and Bacillus of Friedländer (pneumo-bacillus). In collecting specimens for vaccine work, the prostate should be massaged, and if this fails to produce a satisfactory specimen a urethroscope should be used and cultures should be taken from any inflamed lacunæ seen there. The best medium for cultivating the gonococcus is that made under Colonel Harrison's supervision at Rochester Row Hospital, namely, Thompson's Agar-glucose-plasma-Ringer medium, a full description of which will be found in the issue referred to in the appropriate reference (7). Captain Thompson lays stress on the importance of counting the suspension before autolysis occurs, that is, within 24 hours of putting it up. A new line of treatment by Russ (8) has been tried, namely, killing the gonococci by inserting a positive pole catheter into the urethra. Ten to twenty doses are necessary for a cure. Whilst manipulation is slight, the treatment appears to an outsider to be somewhat lengthy, and although it is worthy of extended trial, yet one doubts whether it has many advantages over ordinary methods. Before going into details of the vaccine treatment of urethritis, it will be reasonable to consider whether there is sufficient organic basis to justify its employment, and this is best done by a consideration of the toxins and antitoxins concerned and evoked respectively.

The Toxins and Antitoxins.—According to Emery, the gonococcal toxin is mainly an endotoxin, which is stable enough to resist boiling for some hours.

De Christmas claims to have isolated an exotoxin also, but this is doubtful. (See Sec. III, Chap. II.) Filtrates are usually atoxic. Injection of cultures into lower animals only cause local inflammatory changes, *e.g.* peritonitis. In the rabbit, Towey has produced agglutinins, but this does not apply to man. Towey found that in rabbits a homologous serum clumped gonococci when diluted even up to 1 in 700,000, but a heterologous serum only 1 in 50, which seems to show that in gonorrhœa also autogenous vaccines are likely to be much more effective therapeutically than are stock vaccines. Immunity is not obtained through loss of virulence of gonococci, as recrudescence after an alcoholic debauch is usually of the primary severity.

Prophylaxis.—The question of prophylaxis hardly arises except as regards the complications of gonorrhœa. It is undoubtedly true that early and energetic vaccine treatment diminishes the incidence of complications such as prostatitis and arthritis.

Statistics.—In this case I propose to quote the statistics of those who have had more experience with venereal cases than myself. Unless one is working in a venereal hospital, one does not keep in touch with many acute cases, as they are usually transferred thither immediately after diagnosis. With regard to chronic cases, the same system largely obtains. One, therefore, values others' results more than one's own in this respect.

Brett (9) reports 33 cases of acute gonorrhœa, whose average stay in hospital was $13\frac{1}{2}$ days. If

they were clear for 4–5 days, he pronounced them cured. He used a commercial stock vaccine, the first dose of which was 200 millions of cocci, the second (after 48 hours) 1,000 millions, and the third 1,000 millions after 2–3 days. He finds that the vaccine is unstable and the strains vary in potency, thereby confirming Towey's observations. Kidd (10) states that if cases of gonorrhœa are treated with vaccines the disease merely spreads upwards, thereby denying any virtue at all to vaccines. *Qui vivra, verra.*

Haworth (11) has got excellent results with sensitized vaccines in gonorrhœal arthritis, using fairly large doses. He reports 16 cures out of 17 cases.

Enough has been said to show that there is certainly a case for vaccine treatment in both acute and chronic gonorrhœa.

The Nature of the Vaccine.—Haworth found stock vaccines and autogenous vaccines in one case unavailing. He sensitized his vaccine by using a commercial serum. The actual process he employed was to mix the serum and bacterial emulsion and incubate them for 24 hours at 37° C., and then to remove the serum and replace it by saline. With regard to autogenous vaccines, there is a temptation to ignore them because stock vaccines are so much easier to obtain. My own experience is that autogenous vaccines are much more likely to be effective than are stock strains, as this was proved conclusively by Towey's experiments—and by one's own experience in other fields of vaccine therapy.

The Dosage and Intervals.—For acute gonorrhœa, the dosage and intervals have already been suggested.

In chronic or complicated cases, Haworth recommends the following course: 1st day, 25 millions; 2nd day, 50 millions; 3rd day, 100 millions; 5th day, 150 millions; 7th day, 200 millions; and then increasing by 50 millions every 3rd day up to 550 millions; then increase by the same amount every 5th day.

A second series of cases was tried on the following course:

	Millions of gonococci.
1st day	100
5th ,, ...	200
9th ,, ...	400
13th ,, ...	600
17th ,, ...	800
21st ,, ...	1,000
25th ,, ...	1,200

And increasing 200 millions every 4th day up to a maximum of 2,000 millions. Haworth uses "young" strains (under 4 months old), and claims absence of reaction except rarely. He finds the second routine less troublesome and just as effective. One feels that this method has much to recommend it.

Since a course of treatment does not usually last three months, it is not usually necessary to change the vaccine.

Estimation of Effect.—Both clinical and bacterio-

logical methods can be employed herein if desirable. Therapeutics are becoming an exact science by degrees, and if one can mathematically estimate the ratio of immunity, as one can in gonorrhœa, with an organic type of treatment, as opposed to a chemical type of treatment, then one ventures to think that a very distinct step forward towards the goal of exact therapeutics has been made.

Complement-deviation in Gonorrhœa

The complement-deviation test is an aid in determining whether or no a patient is cured of gonorrhœa. Numerous investigators, of whom the first were Bruch (12) and Meakins (13) in 1907, have elaborated the test. It has now been determined that a polyvalent vaccine must be used as antigen; a positive reaction indicates, according to Schwartz and MacNeal (14), the presence or recent activity in the body of a focus of living gonococci, but a negative reaction does *not* exclude the disease. There are certain important limitations which distinguish it from the Wassermann reaction. If the infection is confined to the anterior urethra, a positive reaction is not obtained. No strong reaction can be expected before the fourth week of the infection, and then only in acute cases with complications.

The quantity of antibody formed is small, and therefore close attention to technical detail is essential. The technique is like the "Original" Wassermann reaction. It is easily explained in general terms.

Consider three factors :

(1) Complement (1 c.c.) = 1 in 20 fresh guinea-pig's serum ;
(2) A 2·5% suspension of washed sheep's cells (1 c.c.) ;
(3) An appropriate dose, say, 0·3 c.c. of diluted hæmolytic serum—

(this is determined by titration)—*i.e.* of horse serum, which will, when mixed with complement, dissolve sheep's cells.

Mix 1 + 2 + 3 and incubate 1 hour at 37° C. Hæmolysis occurs. Now mix—

(1) Complement (1 c.c.) ;
(4) Antigen (0·1 c.c.) (diluted), *i.e.* gonotoxin ;
(5) Patient's serum (0·1 c.c.), containing antibody,

and incubate 1 hour at 37° C., using controls for each factor to prevent "false positive" reactions. If gonococcal antibody is present, complement will be deviated, so that, if to 1 + 4 + 5, then 2 + 3 are added, in other words 1 + 2 + 3 is, if possible, repeated, there being no complement, hæmolysis cannot occur. For further technical details see Kolmer's *Immunity and Specific Therapy*.

The principle of the test is the inability of the reaction 1 + 2 + 3 to occur, if the gonococcal antibody has previously been allowed to absorb complement (reaction 1 + 4 + 5), which it will do only if antigen is present.

Reactions must be guarded against by the sub-

stitution of sensitized vaccines if autogenous vaccines are too toxic. On no account must the surgery of these conditions be neglected. The bacteriologist is only an accessory after the fact of cure.

It is hardly necessary to add that in chronic cases of urethritis of origin other than gonococcal a mixed autogenous vaccine should be employed in appropriate doses. The initial doses should be as follows, roughly:

	Millions.
Streptococcus	25
B. coli, B. proteus	25–50
Micrococcus catarrhalis Bacillus of Friedländer	50
B. influenzæ	100
Staphylococcus	100

The intervals should be 5–10 days, and reinfection with an extraneous organism should be watched for.

CHAPTER X

DISEASE GROUP: INFECTED GUNSHOT WOUNDS

Principles of Specific Treatment

The rationale of vaccine treatment in appropriate cases, as illustrated by a brief allusion to their pathology, with experimental evidence adduced, will be the subject of this chapter. The bacteria which infect gunshot wounds are primarily fæcal in origin, with the possible exception of aërial infection of Bacillus pyocyaneus and by a sporing "air bacillus." There are two groups of germs between which no hard-and-fast line can be drawn, namely, aërobes (oxygen-loving) and anaërobes.

Certain so-called aërobes can flourish anaërobically (the streptococcus and his fæcal affinity, the enterococcus) and so-called anaërobes can grow aërobically, *e.g.* in a Durham's tube (G), as Wolf and Harris (I) have shown to occur with the Bacillus perfringens. Furthermore, the symbiosis of these two groups has been proved to be mutually advantageous, as Douglas has shown. The aërobes contain the following types:

The streptococci, usually S. fæcalis, identical with the enterococcus.

The staphylococci, albus or aureus, seldom the S. citreus.

The colon-group bacilli:

B. coli and its varieties.

B. proteus and its varieties.

B. pyocyaneus and its varieties (blue-pus bacillus).

The anaërobic group is classified by Henry into two groups:

(*a*) The saccharolytic or sugar-splitting group:
The bacilli of gas-gangrene (B. perfringens (B. Welchii), at least four types; B. œdematiens; B. bellonensis var.) (G), and others less important.

(*b*) A proteolytic or proteid-splitting group:
B. tetanus;
B. malignant œdema (G), and others.

The actual mechanism of wound infection in a case of gas-gangrene is explained by Henry in a very illuminating manner.

First of all there is the initial trauma, local death, and a focus for growth, followed by a latent incubation period. Then comes saccharolysis by bacteria, *e.g.* B. perfringens, from muscle-sugar, yielding acid and gas, with inflammatory œdema and anæmia by pressure. Next comes proteolysis by bacteria of group (*b*). Sulphuretted hydrogen and other

volatile malodorous substances are evolved. The red muscle turns black through acquiring sulphide of iron, the iron coming from broken-down hæmoglobin, and toxæmia results from absorption of toxic products of proteolysis, *e.g.* peptone. Bacillus perfringens only enters the blood stream just before death. Now, unless the anti-tryptic power of the body at the site of infection is diminished, the bacillus of gas-gangrene *cannot get a foothold*. The aërobic germs do this, and B. perfringens completes the bad work, sometimes with an almost " explosive " violence.

Wright has shown that there is also in gas-gangrene a local acidosis with later a general acidæmia, the clinical picture of which is vomiting, collapse, excessive respirations, pallor, clear intellect, no suffering, and a body cooling progressively *before* death. Acid-production also is carried on by the liver in cases of metastasis. Once gas-gangrene occurs, the ideal organic treatment would therefore be an *alkalinized anti-tryptic serum* in these cases. I am aware that in a recent War Office memorandum on gunshot wounds such a serum is recommended on the strength of its demonstrated protective powers in animals. I trust it has been shown that the theoretical basis of its use is rational. Major Bull, of the U.S.M.C., has also used a serum of this kind therapeutically (see Part I, Chap. V, Sect. II). But prevention is better than a cure; and if gas-gangrene can be prevented by thwarting the organisms which enable it to get a foothold (and

ordinarily it cannot do so, owing to the anti-tryptic power of the blood), then indeed the matter is worth our consideration.

Moynihan (2), as an independent surgeon, states that, in spite of diversity of opinion, "*no one can deny that a case has been made out for the trial of vaccines in appropriate cases. . . . The streptococcus vaccine is of great value, . . . and the prophylactic virtues [of vaccines] have not been given fair trial.*"

Besides the evidence patent in the pathology of gas-gangrene in favour of vaccines in order to thwart the activities of the aërobes before the gas-gangrene process can get a footing, let me give other pieces of evidence. Dean and Mouat (3) have proved that in cultivation a long time may elapse before the tetanus bacillus appears in cultures in sufficient numbers to be identified. Here again is a germ assisted by aërobic symbiosis in getting a foothold. A side-issue of this consideration is afforded by the practice, initiated at Reading, of sowing wounds with a sporing anaërobe (Reading bacillus), so as to assist their healing. "Similia similibus curantur" with a vengeance! Considering what Dean and Mouat proved, I, for one, should be very chary in introducing any sporing anaërobes into wounds. My object is to get them out of wounds, the sooner the better, for they sometimes contain tetanus amongst their number, as we know to our cost.

There are many reasons why vaccines are likely to do good in infected wounds. Goadby (4), in 1916, quoted a large number of cases with results,

treated by himself and Mr. Jocelyn Swan at the Royal Herbert Hospital, Woolwich. I have had the pleasure of working with two colleagues of Messrs. Goadby and Swan, and, following on similar lines, though not identical, I have had a considerable measure of success. There is no compliment to success greater than imitation, and I am able to record that several independent surgeons have spontaneously requested me to treat certain of their cases with vaccines, and have been pleased and even enthusiastic with the results. I should like to say at once that vaccines are no panacea for infected gunshot wounds; they are only a valuable adjunct to good surgery and good nursing. Many surgeons, I regret to say, despise vaccines, finding their own methods all-sufficient. This is not broad-minded. A fair trial, with controls, is all that is asked for, and what Moynihan said in 1916 is true to-day. Vaccines have *not* had a fair trial.

I will now briefly recapitulate the experimental evidence in favour of a fair trial for vaccines in these cases.

Goadby quotes a number of cases (over 4[illegible]), an analysis of which proves that prophylactic vaccination in the vast majority is effectual in preventing post-operative "flares," *i.e.* rises of temperature with increased post-operative toxæmia, both local and general, phenomena which every military surgeon knows well.

Again, *well-vaccinated cases seldom, if ever, have secondary hæmorrhage.* Goadby quotes 47 cases:

24 of these were vaccine cases and 23 controls. Of the vaccine cases, not one had a secondary hæmorrhage, whilst amongst the controls no less than 10 instances of secondary hæmorrhage occurred. I have come to the conclusion that cases treated by the hypochlorite, and more especially the Carrel-Dakin method, tend to be more prone to secondary hæmorrhage than do cases treated otherwise, in spite of the great value of hypochlorites. The latter are known to exert a solvent effect on dead and dying tissue. Therein lies great virtue and some disadvantage. The virtue is that, since living cells can protect bacteria, as Peyton Rous and F. S. Jones (5) proved, germs may, and often do, survive within phagocytes and granulation cells, and since hypochlorites disintegrate some of these cells the bacteria then lose their protection. Rous and Jones's evidence is so far-reaching in its logical results that I will quote it further.

Consider a specific hæmolytic serum for, say, rabbits' red cells. Add some such cells to a leucocytic suspension at 37° C. Some red cells will be phagocyted. Add then hæmolytic serum. All free red cells will be dissolved, but those within the phagocytes will be protected and undissolved. Using trypan-blue as an indicator of tissue-death, you will find the phagocytes are alive: so soon as they die red-cell lysis occurs.

Goadby, using N/150 potassium cyanide, killed typhoid bacilli in a suspension of guinea-pig's corpuscles. Such a solution does not kill the corpuscles

themselves. Control suspensions of bacteria without corpuscles were negative, but inoculation of the mixed suspension grew typhoid germs because some of the bacilli had become engulfed by the cells and had survived.

Wherefore it follows that phagocytosis is not an unmixed blessing, nor is it always a means of *killing* bacteria. It is, perhaps, merely scavenging. This is a point against Metchnikoff's theory of phagocytosis as being the sole protective mechanism of immunity.

Nuttal and Ehrlich were nearer the truth in assigning to the body fluids the major protective rôle against bacteria. There is much in this. So far as our wounds are concerned, *phagocytosis means continual reinfection.* In dissolving phagocytes and granuloma cells, therefore, hypochlorites do good. But they may thus liberate a clot occluding a vessel and so cause secondary hæmorrhage. Then one is asked, How do vaccines prevent this? They do so, given time, by limiting the spreading necrosis and by exploiting the healthy cells of the body in favour of the unhealthy, causing the former to manufacture antibodies in excess of their individual requirements. In spite of the above, leucocytosis is a natural reaction of immunity. All that has been proved is that living leucocytes do not at first at any rate kill germs. It is another matter when the leucocytes break down.

Lazarus Barlow (6) has shown that in gunshot wounds of the knee an examination of the joint-

fluid is an aid to prognosis, according to the nature of the leucocyte count. A high leucocyte count with a high polynuclear count means a bad prognosis. The absolute number of leucocytes runs parallel to the damage and to the heaviness of the infection.

Before giving my own results with vaccines, it will be well to consider the factors which influence the flora of wounds. Firstly, the phagocytes and granulation tissue may harbour germs. Hypochlorites counteract this. Goadby, cultivating dressing from wounds within half an hour of being treated with—

(1) Hypochlorite solution, got *no* growth;
(2) Iodine solution, got a profuse growth;
(3) Peroxide of hydrogen solution, got a profuse growth;
(4) Saline solution, got a profuse growth.

Secondly, the fibrous tissue around wounds prevents free access of blood and of antibodies; and, thirdly, a sequestrum harbours germs indefinitely. Goadby claims that vaccines increase constitutional resistance and prevent the spread of the damage, as evidenced by the suppression of "flares" and secondary hæmorrhage in well-vaccinated cases. It is the surgeon's business to attend to the mechanical factors afore-mentioned. Without such attention vaccine therapy is useless, and without vaccine therapy surgery is sometimes partly or only very slowly effectual, as I propose to show in the next chapter.

CHAPTER XI

DISEASE GROUP: INFECTED GUNSHOT WOUNDS (*continued*)

The Application and Results of Vaccine Treatment

Prophylactic Vaccination.—A test case was taken at the Military Hospital, Eastbourne, under Dr. Merry. On the 17th of January, 1917, in the afternoon, this patient was given 1 c.c. of a stock prophylactic vaccine of the following composition:

	Millions.
Streptococcus	10
Staphylococcus albus	30
B. coli	60
B. proteus	10
B. pyocyaneus	30, a vaccine made from local strains.

His condition was as follows: there was a septic stump with a projecting femur bathed in pus, and the general condition was bad. His temperature was 99° in the evening of the 17th. On the morning of the 18th he was operated on. The bone was trimmed and the stump thoroughly cleaned, involv-

ing a good deal of manipulation. On the evening of the 18th his temperature was still only 99° F., and on the 19th was normal. This was not what one would call a well-vaccinated case, but there was no "flare," and its absence is significant. The case was chosen by Dr. Merry as a probable "flare" case.

Captain Davis, the chief surgeon at Eastbourne, used prophylactic vaccines in his wards daily, firstly the "antisepsis" vaccine and later some I made for him from local wound germs. Before this secondary hæmorrhages occurred occasionally and fairly regularly, but subsequently I understand that a secondary hæmorrhage was a very rare occurrence in his wards. Goadby's results were found to be correct in these two respects.

Without vaccines "flares" are the rule after operation and secondary hæmorrhages comparatively common. I only recollect one of my vaccine-cases having a secondary hæmorrhage. He had had one injection only, and was having Carrel-Dakin hypochlorite treatment.

Further details will be found in Mr. Goadby's (1) paper in the *Lancet* (see reference), wherein 100 or more cases are quoted, controlled. In my opinion the case for prophylactic vaccines is overwhelming.

Therapeutic Vaccines (invariably autogenous).—Only aërobic germ vaccines are made. By reason of their inherent vitality and spores I consider anaërobic vaccines a contradiction in terms. By

killing the spores you overheat your vaccine. Here it is more difficult to judge results. By observing a large number of cases, with controls, one can obtain scientific evidence in favour of therapeutic vaccination. The other way is to compare vaccine cases with one's general experience of other cases, and to note the fact of cures in cases not amenable to other treatment, *e.g.* very chronic sinus cases.

When a case which has suppurated for months or years is sent for vaccine treatment and heals, as one of mine did in 47 days, one hardly needs a control in adjudging such a case a success on the part of vaccine treatment, this case *having had no other kind of treatment.*

I propose to quote in detail a series of 25 consecutive cases, without prejudice, for the reader to judge for himself. In every case an *autogenous* vaccine was used. (See pp. 80–83.)

It is noticeable that the earlier cases in this series show quicker improvement than do the latter. The earlier cases, Nos. 1–16, were treated at Eastbourne, and were not necessarily the most intractable ; the latter were treated at Netley, which is not so healthy a locality as Eastbourne, and were specially selected intractable test cases. This is a typical series, and the results speak for themselves. I submit that controls are unnecessary. Any military surgeon can form an opinion as to the average duration of treatment of his cases. Consider case No. 3, a naval officer, wounded at the Battle of Heligoland, who suppurated for two years, and then had a vaccine

Case No.	Nature of wound.	Organisms.	Duration of vaccine treatment.	Result at end of such treatment.
1	Septic G.S.W., R. knee	B. coli, Streptococcus; Staphylococcus albus; Staphylococcus aureus	42 days (5 injections)	Complete healing; fairly movable joint
2	Septic G.S.W., R. knee	Streptococcus; Staphylococcus albus; B. proteus type	74 days (8 injections)	Healed; stiff knee
3	Septic G.S.W., R. tibia; compound fracture	B. pyocyaneus	47 days (5 injections)	Healed; walking about; previously suppurated 2 years approximately
4	Septic G.S.W., L. thigh; compound fracture	Streptococci; Staphylococcus albus; B. proteus var.	73 days (8 injections)	Completely healed
5	Septic G.S.W., R. thigh and R. tibia; compound fracture	B. pyocyaneus	47 days (5 injections)	Healed; can walk
6	Septic G.S.W., L. hand	Streptococci	46 days (5 injections)	Healed

7	G.S.W. hand (R.) (septic)	Staphylococcus albus; Streptococcus	39 days (5 injections)	Healed
8	Septic G.S.W. humerus; compound fracture	Streptococcus; Staphylococcus albus; B. proteus var.	35 days (4 injections)	Healed
9	G.S.W. chest (septic)	Streptococci; Staphylococcus albus	1 injection	Died of carotid hæmorrhage; post-operative
10	Septic G.S.W. thigh	B. coli	43 days (5 injections)	Healed
11	G.S.W. chest (septic); lung involved	Pneumococci; Staphylococcus albus; Streptococcus	61 days (7 injections)	Healed
12	G.S.W., L. knee	Staphylococcus aureus; B. proteus var.		Not reported on
13	G.S.W., R. leg; compound fracture of tibia	Streptococcus; B. coli		Not reported on, except "did well"
14	G.S.W. (septic); compound fracture of humerus	Staphylococcus albus; Streptococcus		Not reported

Case No.	Nature of wound.	Organisms.	Duration of vaccine treatment.	Result at end of such treatment.
15	G.S.W. iliac bone; pelvic abscesses	B. coli	Not reported—some months at any rate	Previous to vaccine, severe secondary hæmorrhage, which ceased; improved; thought to be tubercular; lost sight of
16	G.S.W. thigh (septic); subsequently amputated	Staphylococcus aureus; Streptococcus	279 days (24 injections)	Many sequestra; much perostitis; patient nearly died; great improvement; never had secondary hæmorrhage; vaccine twice changed; doing very well
17	G.S.W. tibia; multiple chronic sinuses	B. coli	129 days (14 injections)	Completely healed
18	G.S.W.; compound fractured femur; sinus	B. coli	105 days (13 injections)	Sinus discharged since Oct. 1, 1916; vaccine begun May 2, 1917; completely healed
19	G.S.W. shoulder; sinus	Diplococcus; ? D. magnus of Tissier; Staphylococcus aureus	92 days (11 injections)	Wounded Nov. 7, 1916; vaccine May 8, 1917; sent out healed completely

20	G.S.W., L. arm; open shell-wound	B. coli; B. pyocyaneus	174 days (17 injections)	Striking improvement at first; sequestra delayed healing (two operations); almost healed on exit; no "flares" or secondary hæmorrhage
21	G.S.W. thigh; sinus	B. pyocyaneus	65 days (6 injections)	A septic amputation; stump; quickly cleared up and healed
22	G.S.W. leg; sinus; compound fracture of tibia	B. coli	79 days (8 injections)	Healed completely
23	G.S.W. back; septic sinus communicated with colon	Staphylococcus aureus; B. coli. Latter disappeared when colon shut off by operation	64 days (7 injections)	Healed; no "flares" or secondary hæmorrhage
24	G.S.W., R. eye (removed); sequestra	Staphylococcus aureus	Still under treatment after 61 days	Improving
25	Chronic osteomyelitis; old compound fracture femur; sequestra; G.S.W.	B. coli; then Staphylococcus aureus	Still under treatment after 88 days	Improving; wounded 3 years ago

which cured him in 47 days. Case No. 16 was wasted to an appalling extent; he had so much pain that he almost became a morphino-maniac, was despaired of for days, and now has put on flesh and is able to go down to the seashore in all weathers. Vaccines certainly helped him constitutionally as well as locally. It is a curious fact that one can almost diagnose the presence of sequestra by the way in which a patient reacts to vaccines. Case 20 illustrates this (see result). It will be noticed that I have ignored anaërobic vaccines, *e.g.* a vaccine containing B. perfringens. The reason for this prefaced my remarks. It follows, moreover, from the pathology of infected wounds that, if the aërobes are rendered innocuous, anaërobes such as B. tetanus and B. perfringens cannot get a foothold.

As for tetanus, so for gas-gangrene serum therapy is the rational means of prophylaxis and treatment. (See Chapter IV, Section II.)

It is not reasonable to try to classify the above-quoted cases in terms of the statistician. No two cases are exactly alike, and percentages are out of place. A general idea of the usefulness of vaccine therapy is what has been aimed at.

The author submits that many days, much diminished suffering, and even lives are to be gained by a rational use of vaccine therapy in cases of septic gunshot wounds. In view of the value of man-power to this country, such a question attains an economic importance.

Disease : **Septicæmia**

I have repeatedly tried vaccines in septicæmias of all kinds. Only in the case of puerperal septicæmia have I found them at all availing. Pneumococcal and streptococcal septicæmia cases have not improved. I am aware that others—for instance Allen (2)—claim good results. Nevertheless, I believe that once the germs are in the blood vaccines only lower resistance and a serum is the sole form of organic therapy likely to do good.

CHAPTER XII

DISEASE GROUP: CONTAGIOUS DISEASES

PART I

Diseases: DYSENTERY, TYPHOID, CHOLERA, AND MALTA FEVER

PART II

Disease: TYPHUS FEVER, INFECTIVE JAUNDICE

PART I

General Ætiology.—Inasmuch as these diseases have been correlated therapeutically by Castellani, and often have an identical geographical distribution, it is proposed to deal with them together in one chapter, despite the fact that there is material enough for many.

Amœbic dysentery does not, of course, come within the scope of vaccine therapy, but the bacillary type, due to certain organisms of the coli-typhoid group, does. The organisms involved are usually the Shiga or Flexner bacillus, or, more rarely, the organism known as "Morgan No. 1," or the still less well-known types such as "Y" or "Strong."

The usual organisms of the Enteric group are the typhoid bacillus and the paratyphoid bacilli "A" and "B." These two groups of germs are distinguished by their motility or immotility—the latter group are motile, for instance—their gas-producing powers, certain sugar reactions, their powers of forming indol from peptone, their agglutinating powers with homologous sera, and by certain other traits.

The organisms associated with cholera and Malta fever in all cases are respectively a vibrio and a micrococcus.

Castellani's Vaccines.—Castellani, a noted Italian bacteriologist, devised two valuable prophylactic vaccines—the "Tetravaccine" and the "Pentavaccine." The tetravaccine contained germs of typhoid fever, paratyphoid "A" and "B," and cholera germs, the pentavaccine the same, plus plague bacilli.

Lurie (1) treated 3,000 cases with tetravaccine prophylactically (in 2,000 no case of any of the four diseases appeared, although epidemics of all four were raging), and found the sera of such cases to agglutinate homologous bacilli as strongly as in monovaccines. A mild local reaction only was noted. The pentavaccine in 2,000 cases had similarly good results.

Disease: **Dysentery**

Concerning dysentery, there has been much controversy with regard to the best kind of

vaccine or serum to employ. Dysentery vaccines are ordinarily very toxic. Pratt Johnson and Milne (2) find severe reactions to occur unless a sensitized dysentery vaccine is used, *i.e.* one exposed to the action of anti-dysenteric serum for a time at body temperature. These workers used a mixed vaccine of the following composition:

	Millions per c.c.
Typhoid bacilli	500
Paratyphoid "A" bacilli . .	250
,, "B" ,, . .	250
Dysentery bacilli	250

and using it prophylactically inoculated twice with an interval of eight days in between.

Gibson (3) criticized Dean's method of making an atoxic vaccine by sterilizing with Eusol on the ground that the vaccine became toxic on keeping, because of spontaneous autolysis on the part of the bacilli. He also notes that sensitized vaccines did not stimulate the elaboration of protective substances, owing to antibodies in the serum. He contended that, if one could get rid of these antibodies, all would be well, and an atoxic and effective vaccine could be made. This he claimed to do, and together with Harvey did much valuable work on dysentery and typhoid vaccines. On the other hand, Thompson (4) advocates a vaccine not sensitized, but treated with weak carbolic. The point thus brought forward prominently is the toxicity of the dysentery bacilli, and it will be well for us to consider this fundamental point.

The Toxins and Antitoxins of Dysentery.—A marked absence of clear thinking is noticeable in the numerous writings on dysentery vaccines and sera. Often enough the kind of dysentery is omitted; occasionally we may be told that amœbic and not bacillary dysentery is the subject; but further than this the hapless reader is often left in the dark. The kind of dysentery makes all the difference. One type (Shiga) produces a soluble and extra-cellular toxin (just like diphtheria); a second type (Flexner) does *not* do so.

The strongest poisons are produced by the Shiga variety. Dysentery is a toxæmia, the toxins being absorbed from the intestine. Intravenous injection of toxin in rabbits produces diarrhœa, subnormal temperature, dyspnœa, and paralysis. The gut shows acute toxic features, the toxin no doubt acting locally after excretion. An endotoxin also occurs which is fairly stable. The point to remember is that it is the exotoxin which is by far the most poisonous factor. Shiga dysentery is analogous to diphtheria, being a true toxæmia. Antitoxin has been prepared and used with success in America and Europe, both prophylactically and therapeutically. As one would expect, antisera for the Flexner group are and have been found useless. Vaccines are, nevertheless, indicated for the Flexner group. Bearing this in mind, let us examine certain results of serum and vaccine therapy. Thompson proved that *unheated* vaccines are more effective as tested by the lethal protection they conferred, and they

also appear to be less toxic. Ross and Kauntze (5) also noted the toxicity of heated dysentery vaccines. The possible explanation may be that in heating a certain amount of exotoxin may be formed before the germs are killed.

What is the logical sequence of all this? To my mind it is this. In Shiga dysentery we are dealing with a fairly potent endotoxin and a very potent exotoxin. Therefore *we must combine serum and vaccine therapy.*

Without doubt, a case for chemically sterilized and also for sensitized vaccines made after Gibson's method has been made out. The potent exotoxin also calls for serum therapy. Here we see clearly that a vaccine in dysentery may be sufficient for prophylaxis, but in the disease, where a powerful exotoxin does the damage, as in diphtheria, a serum must be called into play.

Let us therefore examine the evidence in favour of anti-dysenteric serum. We are told that on the whole the bulk of the evidence is in favour. In 1907 Kruse and Shiga independently used sera: the latter used vaccines and sera together. In 1910 Ruffer and Willmore prepared polyvalent sera from Shiga and Flexner strains, giving 40–60 c.c. in mild cases, 80 c.c. in medium, and 100–320 c.c. in 24 hours in severe cases. They noted that in 4–12 hours after injection the pulse and heart sounds improved vastly, the temperature fell, the mental condition improved, the stools became abundant and fœtid, the sloughs became more numerous in

the stools, which subsequently soon diminished in number. In 1913, Willmore and Savage treated 220 cases and noted improvement followed by relapse. No vaccine was simultaneously employed, and so that is what one would expect. It was claimed that at El Tor, in Egypt, the mortality was reduced from 70% to 12%. That is also what one would expect, since the deadly exotoxin was combated.

In the third week of September 1917 no less than 3,802 cases of dysentery occurred in Prussia, with 550 deaths. Anti-serum was employed. Ewald gave as much as 80, 60, 30, and 30 c.c. on successive days to one case, then 50 c.c. ten days later. There was some anaphylactic reaction, as shown by a local painful swelling with pyrexia; but adopting the desensitizing method (see chapter on Anaphylaxis)—that is, giving ½ c.c., followed by 15 c.c. in 4 hours' time, and so on—such difficulties were avoided in other cases. Some cases showed reaction at the first injection of the urticarial-arthritic type, with glandular swelling quite like typhoid, except for the absence of leucopenia. The result of using the serum was presumably a reduced mortality.

The Mediterranean Force Committee went into the question of anti-dysenteric serum, and recommended, on the strength of results following its use in the British Army, 20 c.c. to be given as *early* as possible in the disease. Even 60 c.c. was to be employed in very severe cases. Their rule was to recommend one dose of 10 c.c. in a mild case, two doses of 20 c.c. twice in a day in moderate

cases for two or three days, and 20 c.c. four times a day in the worst cases. The serum was to be given subcutaneously into the flank or intravenously. The results were not so good as Castellani's, the Committee thought, perhaps because some of the cases were of the amœbic type. They were nevertheless good enough to justify the use of the serum. The combined treatment should certainly be given a trial. The pathological evidence points towards this.

Disease: The Enteric Group

Preventive Inoculation.—Prophylactic vaccines for typhoid fever are an acknowledged success, and it is the old Regular R.A.M.C. who primarily established this by their work in India and South Africa. It will not be out of place to quote a few statistics bearing on this matter, chosen primarily from foreign sources.

Courmont gives the following French Army statistics (1916):

	Deaths.
Non-vaccinated cases	17·4%
Of the vaccinated cases:	
Those who had but 1 injection . .	6·0%
,, ,, 2 injections . .	4·0%
,, ,, 3 injections . .	2·5%
,, ,, 4 injections . .	1·9%

Lieutenant-Colonel Webb-Johnson (6), writing on the surgical complications of the enteric fevers, names many, including hæmorrhage, perforation, etc. His figures are striking:

	Typhoid.		Paratyphoid "A."		Paratyphoid "B."	
	Inoculated.	Not.	Inoculated.	Not.	Inoculated.	Not.
Cases .	821	297	123	221	239	799
Deaths .	27	57	None	1	1	17
Mortality .	3·28%	19·19%	0%	0·45%	0·41%	2·12%
Complications	62 instances = 7·55%	106 = 35·69%	1 = 0·81%	24 = 10·85%	14 = 5·85%	123 = 15·39%

Not only does vaccination decrease mortality, but it also decreases the dangerous complications. Castellani (7) raised an interesting point in regard to prophylaxis by mixed vaccines. He utilized a vaccine containing :

	Millions per c.c.
Typhoid bacilli	500
Paratyphoid "A" . . .	250
,, "B" . . .	250
Cholera vibrios	1,000–2,000

The first dose was 0·5 c.c.–0·6 c.c.

The second dose (in 7 days) was 1 c.c.–1·2 c.c.

The third dose (in 7 days) was 1 c.c.–1·2 c.c.

He found by experiment that, whereas rabbits cannot take vaccines of more than three constituents satisfactorily, as judged by agglutinins appearing in their blood-serum, men can. Castellani's vaccine was sterilized by exposure to 0·5% phenol for 24 hours. Another detached point is that menstruation is no contradiction to inoculation. Chantemesse (8) inoculated one arm and vaccinated the other at the same sitting in 3,722 cases, and had no fatalities or abscesses. This occurred at a large Paris clinique.

A similar procedure has often been adopted with my cases, due to necessity, and without any untoward results.

Curative Inoculation in Enterica. In a series of 200 cases the Board of Health of Hungary (9) reports 40–50% to have recovered or improved. These were inoculated within 10–15 days of the onset. Intravenous injections were frequently fatal, and, if employed, sensitized vaccines were recommended.

Fragiuoli (10) found that intravenous injection of 100–300 million dead typhoid germs cut short the disease. Within one hour there was a rigor (105° F.), but within a day the temperature falls to about 90°, with sweating, and after that the patient was convalescent. No unpleasant symptoms were noted. This writer seems of a somewhat perverse disposition, for he reports treating paratyphoid "B" cases with typhoid vaccine and typhoid cases with Bacillus coli vaccine: why, one cannot think.

Gay (11), an American, used sensitized typhoid vaccine, and managed to convert leucopenia (which is a character of typhoid fever) into a leucocytosis of 20,000–40,000 per c.mm. 300 millions is the dose he recommends.

Kennedy and Russell (12) prepared an autogenous vaccine from a case of relapsing paratyphoid "A." Under its use the serum agglutination powers for this germ rose from 1 in 40 to 1 in 1,000. Very small doses of vaccine, only 20 millions to 120 millions, were given. The attacks persisted, but the apyrexial period lengthened. Whether the vaccine raised the

agglutination titre or whether it was the natural reaction of immunity is not apparent.

On the other hand, Drought and Kennedy (13) treated an acute cystitis due to paratyphoid "B" with hexamine and vaccines with complete success. Acute cystitis of uncomplicated origin does extraordinarily well with vaccines (autogenous, of course). Paratyphoid "B" cystitis is no exception. The early condition of this case was indicated by the following signs: pains on and off, frequency of micturition with tenesmus, temperature 100° F., and pulse 112; albumin, pus, blood, and hyaline casts were present in the urine. Evidently there was renal infection to boot.

The following doses were employed and progress reported:

First dose	(13.1.17) . .	50 millions.
Interval 3 days	(15.1.17) . .	Agglutination titre 1 in 100.
Second dose	(16.1.17) . .	100 millions.
Interval 7 days	(18.1.17) . .	Pus enormously diminished; urine sterile.
	(20.1.17) . .	No symptoms.
	(22.1.17) . .	A few pus cells present still.
Third dose	(23.1.17) . .	250 millions.
Interval 6 days	(27.1.17) . .	A trace of pus.
Fourth dose	(29.1.17) . .	500 millions.
Interval 15 days		Slight local reaction; serum agglutinated 1 in 400.
	(5.2.17) . .	Urine sterile.
Fifth dose	(13.2.17) . .	1,000 millions.
Interval 11 days		No albumin; few pus cells.
	(20.2.17) . .	No pus.
Sixth dose	(24.2.17) . .	1,500 millions.
	(10.3.17) . .	All clear; stools *negative throughout*.

This is a very well-reported case, and might be taken as a standard of treatment and control of *any* case of pyelo-cystitis due to coliform bacilli. That is why I have taken the liberty of quoting it in full.

The French, as exemplified by Rathery (14) and others, have used curative vaccines in paratyphoid "B" fever. Of 1,088 cases at the Zuydcoote Hospital, 147 were treated with vaccines. Their conclusions are that the treatment is useful, it always improves the general condition and often shortens the fever, and has never led to harmful results so far.

Koehler (15) reports the interesting fact that a fæcal carrier excreted germs for six months. Gildemeister (16) recovered paratyphoid "B" from a fistula of the arm which was agglutinated by the patient's serum, diluted 1 in 200 parts. Vaccines might well have been employed in both cases.

Mollow (17), another German, used a sensitized vaccine in 140 cases intravenously. The temperature fell at once by crisis or lysis, but agglutination tests were negative. Unfortunately there is a certain slovenly inaccuracy about the report of this otherwise valuable piece of work.

Nevertheless there is a unanimity about these results which suggests the advisability of further trial of autogenous vaccines as a cure for the enteric fevers. Typhoid serum is generally acknowledged to be useless, which, after all, follows from the consideration that the typhoid toxin is an endotoxin, and typhoid fever a bacillæmia at any rate in the early stages. The intravenous method of employ-

ment of typhoid vaccines appears to be somewhat dangerous.

Beyond Castellani's work, referred to above, which is solely concerned with the prophylaxis of these diseases, the author is not aware of any results by way of vaccine or serum therapy in these instances.

Part II

Disease: **Typhus Fever**

Although the causative organism of this fever is an unknown quantity, it is known that the virus can be transmitted from animal to animal. The serum of a cured man or animal is said to be effective prophylactically but not curatively.

Nicolle and Blaizot (1) injected intravenously first leucocytes, then pounded spleen and supra-renals of guinea-pigs into horses and asses, producing anaphylaxis. They immunized an ass by 114 injections in 14 months and a horse by 91 injections in 10 months, and found their serum to be both protective and curative in guinea-pigs and monkeys. Potel and Poirson treated 38 cases, and only 1 died, which was previously tubercular. They found that the serum lowered pyrexia, lessened the severity of the nervous symptoms, and improved the general condition. The early use of 10–20 c.c. daily till afebrile is recommended, and the results are highly promising.

Plotz (2) and others claim to have isolated the causative germ of typhus, which they call Bacillus

typhi exanthematici, and employ a vaccine of fifteen different strains. They vaccinated 5,251 cases, and only 3 cases of these contracted typhus in a severe epidemic ; later figures were 8,420 cases inoculated with 6 instances of incidence.

There is an interesting pseudonym known as the **Weil-Felix reaction.** The serum in cerebro-spinal fever and typhus fever often agglutinates strains of B. coli and B. typhosus ; it probably indicates a secondary infection by those germs. The Micrococcus melitensis (Malta fever germ) is also sometimes agglutinated by typhus case serum.

Wilson (3), of Belfast, pointed out that he noted this before Weil and Felix. Another interesting point which Wilson points out is that the urine of typhus cases often grows the enterococcus (G), which is also often recoverable from the urine of many trench-fever (G) cases. Both diseases are said to be conveyed by the louse. Such is the modern evidence concerning the efficacy of therapeutic and preventive inoculation in typhus fever. It is very inadequate, but this is inevitable, for the disease is relatively rare, and the treatment cannot be put on rational lines until more is known concerning its pathological basis.

Disease : Infective Jaundice

In regard to the infective jaundice prevalent at the Dardanelles, Martin (4) reports that no parasites were found in blood films during the disease. Blood

cultures, he states, were sterile unless jaundice supervened during typhoid or paratyphoid fever; at any rate, the paratyphoid bacillus does not spread up the bile-ducts. In fatal cases, hepatitis and necrosis of liver cells were noted. Hurst holds the same view, namely, that in this epidemic the paratyphoid bacillus was the causative agent. In France, Leslie (5) reports typhoid and paratyphoid *following* infective jaundice with positive agglutination to paratyphoid "A" in one case.

It is a pity therapeutic vaccines were not used in these cases. Then there is **Weil's disease** proper, another Teutonic pseudonym, for Larrey and other Frenchmen discovered the entity known by that name. Inada and Ido (6), who discovered the causative organism, a spirochæte, have experimented with the serum of a cured guinea-pig and found that the spirochæte was digested by it. Immunized goat's serum, they found, cut short the attack in the guinea-pig. (Salvarsan was useless.) Thirty-three cases were treated; 10–60 c.c. were given within 24 hours intravenously, with these results:

	Serum Cases.	Ordinary Cases.
Mortality . .	17% .	31%

They found that 40–60 c.c. bacteriolized all spirochætes within 6–24 hours in the circulating blood. Immune bodies appeared two days earlier in serum cases. In fatal cases fewer spirochætes were found. There was no definite effect on the fever, jaundice or hæmorrhagic tendency. They

found that ordinarily immunity persists for eight years, and consider this a suitable field for serum therapy.

The disease in France is quite distinct from the Gallipoli disease, but is held to be the same but less virulent than the **Spirochætosis ictero-hæmorrhagica** (G) of Japan, described and treated by Inada and Ido, and is therefore worth our attention.

Serum therapy has inevitably crept into this chapter. A consideration of dysentery shows that one cannot draw a hard-and-fast line between the two methods of organo-therapy to be considered. Spirochætal jaundice affords a still further instance. The main point to remember is that the line of treatment must in all cases be based on pathological facts. *Exotoxins demand sera, endotoxins vaccines:* a germ which forms both demands both. The Spirochæte we have just been considering evidently forms an exotoxin, judging from results, but I am not aware that this point has been indicated otherwise than by analogy.

CHAPTER XIII

DISEASE GROUP: DISEASES OF SPECIAL SENSE-ORGANS

Diseases: **Diseases of the Eye**

Acute conjunctivitis following a gunshot-wound injury to the adjacent face and involving the conjunctiva often becomes chronic. In one of my cases the infective agent was the Bacillus coli. Vaccine therapy is applicable to such cases, just as it is applicable to other septic wounds. Owing to poor vascular supply, vaccines in eye cases must be applied in full doses. Following removal of the eyeball, a chronic conjunctivitis and dacrocystitis supervened. This case was very obstinate, and one came to the conclusion that one might have missed one of the infective agents. Such proved to be the case, and due improvement followed on making a fresh autogenous vaccine. Sequestra are by no means uncommon in such cases, and failure of vaccine therapy may suggest their presence, if otherwise undiscovered.

With regard to **acute pneumococcal** and **gonorrhœal** conjunctivitis with **hypopyon ulcer**, Allen (1)

advises early and vigorous vaccine therapy and claims good results. The eye should be well washed out previous to taking the culture, with sterile water. Corneal ulcers he also treats with vaccines.

The infecting organisms in such cases are usually one or more of the following:

Staphylococci Streptococcus pyogenes	Septic group
Bacillus coli ,, pyocyaneus ,, Friedländer	Coli-typhoid group

Gonorrhœal conjunctivitis, including **ophthalmia neonatorum,** sometimes clears up very rapidly, but full doses must be given. For example: 100 millions on the first day and 250 millions on the eighth. A cure is sometimes effected in a fortnight. **Chronic angular** conjunctivitis of the Morax-Axenfeld diplobacillus type yields excellent results, so Allen states. He begins with 100 millions, and the dosage is as for the gonorrhœal type. Bryan cured one case of ten years' standing with an autogenous vaccine. It took six months, but he only employed very small doses.

Chronic dacrocystitis usually yields streptococci, pneumococci, or staphylococci. The pneumococcal corneal ulcer, even with hypopyon, is said to do well with vaccines, as also is the "Ulcer serpens corneæ" due to Micrococcus catarrhalis. Herbert Parsons (2) has not found vaccines or sera of much use in eye work. Römer's anti-pneumococcal serum

for hypopyon ulcer he found disappointing, likewise anti-gonococcal serum for ophthalmia neonatorum and gonorrhœal ophthalmia. This leaning towards sera rather than vaccines is no doubt due to the successful results from the use of diphtheria anti-toxin in diphtheria of the eye. Certainly it is not based on the toxicology of the infecting organisms. Therefore one leans rather to Allen's teaching, since he has had extensive experience at the Royal Eye Hospital with the vaccine treatment of such cases.

This much at any rate is certain—namely, that the results of vaccines in these cases justify a more extended and impartial trial than they have hitherto received.

Diseases : Diseases of the Ear, Nose, Throat, and Mouth

On the whole, **otitis media** has not been a successful field of operations for vaccine therapy. There are two reasons for this. One is the frequent presence of dead bone, the other avascularity of the parts. Mollison (3), however, reports good results in a prolonged case of mastoiditis, primarily acute, from a streptococcal vaccine.

Acute rhinitis, yielding influenza and many other germs, does well from the point of view of prophylaxis —witness the multifarious commercial vaccines on the market. There is a point which was established by Dr. Coleman (4), writing from the general practitioner's point of view, that **chronic nasal** or post-nasal

catarrh due to the **pneumococcus** does most excellently well with vaccines. A deafness of many years' standing was much improved by him. It was due to a pneumococcal catarrh. Then there is the **chronic tracheitis** of older folk, which comes under the same category. **Non-pneumococcal** varieties of these complaints do well, but not so well. Rowlette (5) also, reviewing vaccines from the general point of view, classes prophylactic enteric vaccines and recurrent respiratory disease vaccines together as examples of the greatest successes achieved by vaccines.

Hay fever is due to the pollen of Phleum pratense. If the latter be extracted with water (1 gramme to 50 c.c.), this strength is arbitrarily equal to 20,000 units of toxin. The following doses are prepared: 5,000, 1,500, 500, 150, 50, 15, and 5 units per c.c. Individuals vary widely in susceptibility—hence the range.

Two or three drops are placed in the conjunctiva. In a few minutes a reaction occurs. If not, a higher strength is tried until susceptibility is demonstrated, and the initial dose is $\frac{1}{3}$ c.c. of the strength used upon the eye to produce a positive reaction.

Allen, who describes this clearly, states that for protection the initial dose is repeated in eight days, and so on every eight days, until the eye does not react to the former minimal dose. For treatment the first dose is half the above, namely $\frac{1}{6}$ c.c., repeated every five days and increased gradually. This is a highly scientific piece of work. Results

are good. If the patients do not escape, they only have mild attacks.

Pyorrhœa alveolaris should not be treated with vaccines unless the teeth are not decayed or if it persists after extraction. A strict distinction should be made out between a **gingivitis** and a pyorrhœa. The former in soldiers may be due to Vincent's bacillus (B. fusiformis with spirochætes).

Sections of the gum prepared in two such cases showed deposits of brown granules corresponding to the blue line in the mucous membrane, which Major Snowden, R.A.M.C., suggested were due to the bismuth in the B.I.P.P. with which such patients had been treated in connection with wounds. X-rays have confirmed this. The blue line appeared opaque. Whether bismuth predisposes to Vincent bacillus gingivitis is not a settled point, but is worthy of debate. The anaërobe in question is not a suitable germ for vaccine work, but a serum might do good, if powdered Neosalvarsan fails.

Arthritis due to pyorrhœa occasionally does well, but dental attention is of more importance than vaccines in such cases. True Vincent's angina is not a suitable field for vaccine therapy. In earlier chapters I have given reasons why I think vaccines from these anaërobes are likely to be dangerous and ineffectual.

CHAPTER XIV

DISEASE GROUP: DISEASES OF THE RESPIRATORY SYSTEM

Disease: **Actinomycosis**

This disease is due to the ray-fungus, and **mediastinal actinomycosis** is one of its most dangerous manifestations. The treatment is the same in other cases—as, for example, when it affects the **mouth or parotid gland.** Malcolm recently reported a case of the former (1) where the growth presented a boggy swelling in the præcordial region of two years' standing and due to the ray-fungus. Rib resection and massive doses of iodides had no effect. There were two sinuses and a nodule on the pericardium. Weekly injections of $2\frac{1}{2}$ million actino-fragments up to 10 millions were given. Overdose was produced by 10 millions, and was evident by malaise and anorexia with local reaction. The nodule referred to receded. Fifty doses of 4–5 million fragments were given in all. The discharge lessened and the sinuses healed, and the patient was cured. The case was reported in the latter half of 1916. Dean (2), in 1917, cured a jaw case with parotid actinomycosis

in a boy of 18. He advises taking the specimen with a dry swab. Curettage with a sharp instrument tends to spread the involvement. Dean gave 3–10 million fragments weekly up to 25 millions. Only slight reaction occurred with the latter dose. The case was cured except for slight œdema of the cheek, possibly due to fibrosis involving some veins. Four injections of 25 millions each were given. *In less than one month the case was cured.* Moreover, he remained cured. Here vaccines have led to brilliant results. Unfortunately, the isolation of the fungus is sometimes very difficult.

Diseases: **Bronchitis and Laryngitis**

Until recently comparatively unrecognized, the entity known as **purulent bronchitis** has been occasionally epidemic amongst British troops in France. It is characterized by a very high mortality and untoward symptoms—*e.g.* severe cyanosis. Abrahams (3) and others state that the bacteriology of the disease consists of an invasion by the bacillus of influenza, which raises the virulence of the pneumococcus. The influenza germ is the epidemic factor, and Hammond (4) thinks vaccines are likely to do good if given *previous* to bronchiole obstruction. Allen (5) is more optimistic. He recommends an initial dose of 100 millions pneumococci with 200 millions of influenza germs. He states that 10% of the cases are never likely to be fit for service again, and that it is doubtful whether even 30–40% of apparent recoveries do not come under the same category.

The unpleasant sequelæ are malaise, tachycardia, neuritis, myalgia, and gastric disturbances. It therefore appears that, in view of the seriousness of this complaint, all therapeutic agents, including vaccines, should be employed until they are shown to be unavailing.

Chronic bronchitis is common in military medicine. Many cases of obscure origin with mysterious bouts of indeterminate pyrexia with definite chest signs are to be found in many hospitals. I have tried vaccines in such cases with very fair results. Four consecutive cases in hospital showed the Staphylococcus aureus in the sputum. Two cases of empyema likewise showed it. Here is the detailed history of one case. The patient had chronic bronchitis for one year and lately an empyema. Organisms: Bacillus of Friedländer and the Staphylococcus aureus.

	Millions of each.	
1st day . .	50	Temperature 100° F. at night; cough and sputum excessive; empyema discharging.
10th ,, . .	100	No nocturnal pyrexia; no sputum or cough; empyema nearly healed.
20th ,, . .	150	
30th ,, . .	200	
40th ,, . .	300	Empyema healed.
50th ,, . .	400	Quite well; no positive physical signs.

In another empyema case the primary cause was a Staphylococcus aureus isolated from a carbuncle

on the forehead, followed by pleurisy and empyema. The germ was recovered from the blood and from the pus of empyema. The case has recovered.

Another case yielded Staphylococcus aureus and a pneumococcus, and has put on flesh and improved otherwise after being stationary for months. He had bouts of pyrexia of unknown origin, for which no malarial parasites or other cause could be found, and his physical signs are rapidly clearing up under treatment by an auto-vaccine. One of my cases had Bacillus coli and Staphylococcus aureus in the sputum. This one also did well. It would be interesting to know whether these cases, for one was a nurse and five others were in wards containing surgical cases, became infected by wound-germs. If so, this would be a strong argument for more complete segregation of medical and surgical military cases than is now possible.

Laryngitis not due to tubercle, syphilis, or malignant disease is a similar case to bronchitis as regards the results and treatment by auto-vaccines.

Disease: **Pneumonia**

Not until quite recently has serum been found useful in pneumonia. (See Chapter V, Section II.) Moore (6) found the combined use of optoquin (a quinine derivative) with anti-pneumococcal serum to protect mice against the pneumococcus. This treatment has not been tried in man.

What of vaccines? Coleman, representing the

general practitioner, concludes that vaccines in pneumonia are never harmful and may do good. Teale and Embleton claim good results in some cases. Personally, I believe the infection *locally too massive* to permit of vaccines having any appreciable effect when in the consolidation stage. Earlier than this one may do good, but few clinicians diagnose pneumonia sufficiently early for this purpose.

Recent work by F. S. Lister has placed the great value of *preventive* vaccination for pneumonia in native labourers in France upon an unassailable foundation.

In delayed resolution vaccines do much good. One should start with 50 millions and work upwards, dosing the patient every week. In non-tubercular broncho-pneumonia good results have been obtained.

With regard to **pleurisy, empyema,** and **pneumococcal septicæmia,** the first and last are inadmissible to this category, since in the former a truly autogenous vaccine cannot be prepared with certainty, and in the latter the infection is too far gone. It would be as useful in the latter to give vaccines as a trumpet-call would be in the desert. Ordinary septic empyemata of chronic duration do well with vaccines, as shown above.

Disease : **Influenza**

Ætiology.—The evidence that the influenza bacillus is the cause of the disease rests mainly on the fact that it is always present in the secretions of the respiratory tracts in true cases. It is certainly

pathogenic, and my own (7) observations possibly throw some light as to its mode of intoxication. We cannot yet maintain that its causal relationship to epidemic influenza is completely established. The virus behaves like that of scarlet fever and like that of poliomyelitis. Further evidence is needed to show whether it is a true filterable virus, however.

Prophylaxis.—Prophylactic vaccines are useful. One attack of influenza predisposes to a second. Stock vaccines may be used; 50–100 millions should be given weekly for two or three weeks. The serum therapy of influenza, especially influenzal meningitis, is dealt with under "Auto-Sera." (See Section IV.) Both the toxicology and other things show many points in common between this disease and diseases due to filterable viruses.

CHAPTER XV

TUBERCULINS

THE evidence for and against tuberculin (G) as a specific cure has been ably dealt with by Dr. Batty Shaw in one of his papers (1) which appeared in the *British Medical Journal* in the early part of 1913. In view of the fact that unanimity of opinion on this matter is non-existent, it will be well to get back to fundamentals and examine Koch's own experiments, performed so long ago as 1890–91, and then later to see whether his results have borne fruit. What Koch claimed and what he proved are two very different matters. He claimed "that in guinea-pigs, animals known to be more than ordinarily susceptible to tuberculosis, under the influence of tuberculin, although suffering from general tuberculosis, even to a high degree, the morbid process can be brought completely to a standstill without the body being in any way injuriously affected." This is the claim. We all know it has not been vindicated. Nevertheless it behoves us to see what experimental evidence in favour of tuberculin Koch adduced. In 1891, in a well-known German

periodical, Koch gave further details, of which I will, with Dr. Shaw's permission, quote the translation.

"If a healthy guinea-pig is injected with a pure culture of tubercle bacilli, the inoculation puncture as a rule closes and in the beginning appears to heal; in the course of 10–14 days a small nodule occurs which soon breaks through the skin, forming *an ulcer which lasts until the animal dies.* Quite a different result occurs if a guinea-pig which is already tuberculous is inoculated, especially if the inoculations take place 4–6 weeks after the first one. In such an animal the site of inoculation at first closes as in the above instance, *but no small nodule forms*; on the next or following day, *a peculiar change takes place at the site of the inoculation. This becomes indurated and darker in colour, and these changes spread over the neighbouring parts until the total area measures about* 0·5 *to* 1 *cm. across. During the next days necrosis of the skin takes place, and there remains a superficial ulcer, which ordinarily heals quickly and permanently without the neighbouring lymphatic glands being infected.* The injected tubercle bacilli act quite differently upon the skin of a healthy as compared with a tuberculous guinea-pig. This striking change does not belong exclusively to living tubercle bacilli, but occurs just the same with dead tubercle bacilli, whether they have been killed by prolonged low temperatures, or by heat, or by certain chemicals."

N.B.—The animal nevertheless died (this is

usually omitted). Lowenstein, who was responsible for the therapeutic application of tuberculin to man, and other advocates—*e.g.* Römer, Roepke, and Bandelier—all fall back on this paragraph as proof of the curative powers of tuberculin. But Dr. Shaw gives further evidence. He points out that the above was only an example of the Von Pirquet test. Koch found that if the second inoculation of a tuberculous guinea-pig was a large one the animal died. This was a case of anaphylactic death (see chapter on Anaphylaxis).

The point which now remains and is crucial is that Koch said he observed that if small, frequently repeated doses of tubercle bacilli were injected into a tuberculous guinea-pig, not only did the animal's general condition improve, but the ulcer at the site of injection *showed favourable retrogressive changes, and the disease was brought to a standstill in the animal.* It was, in fact, cured.

Here is the definite experimental evidence in favour of therapeutic tuberculin.

The simple fact of the matter is that *no one has yet been able to repeat Koch's experiment successfully. There is no evidence but Koch's in favour of tuberculin as a therapeutic cure for tuberculosis in guinea-pigs, calves, or in man.*

Koch was an optimist. We commonly use tuberculin in the laboratory for weeding out tubercular guinea-pigs. It certainly does this effectually and in small doses, by killing them. No one but Koch has been able to cure an infected guinea-pig by the

use of tuberculin, whether old tuberculin (T.A.) or second tuberculin (T.R.) or the vaccine (B.E.) or the albumen-free tuberculin or bovine or avian or any other tuberculin. There is no question that tuberculin can do infinite harm; scores of people have died prematurely at its hands, and there is no evidence save Koch's that it can do good. Never was there such a commercial vaccine as this one, and never has there been such a gigantic hoax. Is it not a certainty that if bovine tuberculosis could be cured by tuberculin that numbers of cattle would not be slain every year in order to stamp out tuberculosis as they are slain, or that a National Health Sanatorium Scheme for the treatment of tuberculosis should not be found a necessary place in the National Health Insurance Act, as it has been found a place and a very important one too? There is not even unanimity amongst veterinary surgeons as to the value of the evidence for using prophylactic vaccination in calves, and there is no attempt whatever to vaccinate tuberculous cattle therapeutically. In most modern text-books of medicine these facts are ignored. As Dr. Shaw pointed out in his excellent paper, on one page of a certain book we are told that when the tuberculous guinea-pig was injected with subsequent doses of tubercle bacilli the ulcerating wound formed where the *first* injection was made, which in turn caused the guinea-pig to become tuberculous, healed as a result of the second injection, and yet on a later page the author says it was the small, superficial necrosis of the *second*

site of inoculation which healed! Such confusion does not help us in these matters.

Sufficient, I think, has been said to show that the therapeutic use of tuberculins is neither justified by use nor does the experimental evidence on which it is based bear repetition. Wherefore tuberculin should not come within the range of practical vaccine therapy. Whatever good results are imputed to tuberculin must have occurred in spite of it, for its virtues are founded upon experiments which cannot be repeated.

SECTION II

SERA

CHAPTER I

ANAPHYLAXIS AND SERUM DISEASE

Anaphylaxis (translation = without protection) is defined by Wyard as "*Greatly increased sensitiveness of the animal organism to the injection of foreign protein, so that injections of the latter in amounts innocuous to controls produce in the hypersensitive animal symptoms of varying intensity and even acute death.*" Serum, being a protein, comes under this head, but other proteins can do the same damage—for instance, egg albumen, milk, or bacteria. Fortunately vaccines are not usually given in sufficient quantities to be dangerous from this standpoint. The history of the discovery of anaphylaxis is apt to be confusing, so will be ignored and only the essentials considered. The first or sensitizing dose need only be very small, even 0·000,001 c.c., and the more toxic the proteid the smaller the dose necessary. The second or toxogenic dose must be 100 or 1,000 times larger unless the antigen (protein) is toxic. Twelve to fourteen days must elapse before anaphylaxis sets in, except where it is idiopathic, *i.e.*

occurs at once on the first dose. The route is important. The most certain methods are, in order:

(1) Intracerebral and intravenous injections;
(2) Intramuscular;
(3) Intraperitoneal, intrapleural, and subcutaneous injections;
(4) Intrathecal.

The shock varies in severity in different animals. The onset is sudden, often within a few minutes of the injection. In man there are three forms of anaphylaxis, comprehended under the term "serum disease."

First Type.—After a single, large dose of serum, occurring 8–12 days after injection, consisting of urticarial and other rashes, joint pains, glandular swelling, pyrexia, and slight albuminuria. The symptoms depart in 12–48 hours. Rarely fatal.

Second Type.—Appearing 4–8 days after the *second* injection. The same signs and symptoms, but more acute. Return to normal after 12–18 hours. Rarely fatal.

Third Type.—The patient, within a few minutes up to half an hour, becomes uneasy, respirations increase. Double incontinence may occur. There is great muscular weakness. Cough, continuous or paroxysmal, of the dry type occurs. Respiration becomes more laboured; the chest remains expanded. Cyanosis occurs. Death may occur in convulsions or coma. Breathing becomes shallow and ceases. Alternatively, recovery occurs gradually. Local

changes may occur—for instance, œdema of the whole arm, with heat and redness.

The toxin, which is elaborated by the liver, acts on the nerve-endings or muscles of the bronchioles. Drugs appropriately acting on these muscles counteract the effects. Peptone poisoning is very similar. Injected serum of an anaphylactic animal can impose anaphylaxis upon a healthy injected animal. A condition of anaphylaxis may last over three years.

Man is less susceptible than guinea-pigs and more so than mice to this condition.

After considerable doses, often repeated, anaphylaxis may appear within 4–5 days, whereas after 2 or 3 small doses it may be absent after a month. A single injection of 3–5 c.c. does not sensitize as a rule.

The most satisfactory theory of the phenomenon of anaphylaxis was propounded by Friedberger and elaborated by Teale and Embleton. Complement, a thermolabile part of serum, is found to be absent from the blood during anaphylaxis. Friedberger holds that the first injection of antigen brings about an increase of the corresponding antibody, as in vaccines. This antibody, in the presence of complement normally contained in the blood, immediately reacts with the second dose of serum (antigen) and liberates what is called "anaphylatoxin," a toxin, the cause of anaphylaxis. This is only a repetition of the mechanism of the Wassermann reaction. The subject is not fully worked out, but this much is clear.

Practical Considerations.—In these days of anti-tetanic serum it must be assumed that every man who has had an injection more than 14 days previously is potentially anaphylactic. Quite often the medical officer may be confronted by a patient with a septic wound who has gone beyond his period of grace of fourteen days. The question arises as to the right thing to do. The Army authorities have laid it down that to withhold anti-tetanic serum is unjustifiable in face of the danger of that terrible disease, tetanus. Moreover, a case may have early signs of tetanus.

It has been found that starvation will desensitize in 4 or 5 days, but in both cases, especially the latter, this is obviously out of the question. Again, vaccination—that is, by the introduction of small doses of serum during the incubation period, about the 7th to 9th day—will protect against anaphylaxis, but in our case it is too late in the day to do this. If 5–10 c.c. per rectum are given, the patient will be desensitized in 10–12 hours; or if very slow, subcutaneous infusion is employed. The best way is to give a sub-toxogenic dose, *i.e.* one below the minimum required to produce anaphylaxis.* Therefore 0·5–1·0 c.c. may be given as a preliminary injection, followed in six hours by any further dose required or alternatively increase the dose slowly every 10 minutes.

With regard to anti-tetanus serum as used in the

* Or, alternatively, a full dose given under general anæsthesia (Besredka's method).

British Army, Wyard states that an interval up to five weeks between two doses will never give rise to symptoms. This does not apply to cases which have had massive doses. Should shock of this kind occur, atropine, adrenalin, chloral hydrate, and oxygen should be tried.

In the first two cases intramuscular or intravenous injection should be employed. If necessary, artificial respiration should be resorted to. The local reaction is relieved by fomentations, and the irritation by 1 in 100 carbolic or an ointment of this composition, which the author has used with success:

℞ Sulphur precip.	grs. xx
Acid. salicyl.	grs. x
Benzoated lard	ad ℥j

Wyard's article (1) in the *Lancet* has been abbreviated and utilized herein (with apologies), as the author considers it a classical exposition of this matter.

It is of historic interest to note that the first person to record anaphylaxis was an Englishman, Edward Jenner, in 1798. Then came Magendi's work in 1839, and sixty-five years later that of Theobald Smith. Other workers concerned in the elucidation of this puzzling problem were Brieger in 1895, Behring and Kitasato in 1901, also Hericourt and Richet, Gay and Southard, Friedberger, Whete, Teale and Embleton, Wyard and others, and last but not least Harvey and others of the British Army Medical Department.

CHAPTER II

FILTERABLE VIRUSES: POLIOMYELITIS—RABIES, ETC.

This section may, at first sight, seem out of place in a book which aims to avoid the intricacies of indeterminate bacteriology, but the author ventures to suggest that the subject concerned, though of recent development, promises to be extraordinarily significant in the near future. Every practitioner is familiar with infective diseases whose cause is at present unknown—instance smallpox—but in which the virus is capable of transmitting the disease. It is upon such obscure diseases that a study of the filterable virus is likely to react, and in that statement lies the author's apology for including this chapter.

Some very brilliant and original work has been done by Dr. Hort, who is not by way of being a professional bacteriologist, but a Harley Street consultant, and whose work has been criticized on that account. Nevertheless, Darwin was of the same type—an amateur, as Professor Adami pointed out. Wherefore this work is all the more to be commended.

Dr. Hort's original article (1) on the life history of bacteria is beautifully illustrated and well worth detailed perusal. The point sought out and demonstrated was that pathogenic bacteria, amongst which were certain bacilli of the typhoid group which this worker took for examples, outside the body, are capable of giving off living units so minute that they are filterable through bacterial filters such as the Chamberland " F " candle.

In relation to typhoid fever it has long been known that an inoculated stock culture will not reproduce the lesions of the disease. Again, the bacillus of swine fever (B. suipestifer) does not reproduce hog-cholera. On the other hand, bouillon filtrate of its culture through a " B " or " F " Chamberland candle will set up the disease. Again, Hort and Caulfield (2) found that cultures of the cerebro-spinal meningococcus, if injected, do not produce cerebro-spinal fever. Flexner claims to have accomplished this, but he used enormous doses, and probably it was the endotoxin of autolysed cocci which caused the symptoms. In a disease known as the pleuro-pneumonia of cattle, the germ of which is unknown, the filterable virus will produce the infectious disorder, and the virus is capable of growth, as evidenced by clouding of fluid media which is inoculable on monkeys with a positive result.

Hort says that in cerebro-spinal fever the filterable virus and the cocci are two phases of the same disease. One more example: In tuberculosis microscopical tests for the tubercle bacillus may be

negative, and yet inoculation will often yield tubercle in animals previously atubercular, as shown by their remaining healthy when injected with old tuberculin. Filterable viruses, moreover, if heated to 60° C., become innocuous, and therefore are not sporing forms. Scarlet fever, mumps, chicken-pox, and smallpox probably will all furnish filterable viruses. In Hodgkin's disease certain granules known as Much's granules are to be found, also in tubercle, and as Adami showed (3) in hepatic cirrhosis. In order to see them one requires a $\frac{1}{18}$ inch objective. In hepatic cirrhosis the Bacillus coli was grown from material in which these granules were seen. In the light of this work the ætiology of cerebro-spinal fever is not fully explained by the presence of the meningococcus, nor is scarlet fever fully explained by the existence of the Streptococcus scarlatinæ. It will no doubt also give heart to the general practitioner to know that something is being done towards the elucidation of trench fever and of those household diseases such as mumps, measles, and chicken-pox. Possibly also this work on filterable viruses will enable us to apply vaccine and serum therapy upon more exactly scientific lines than has hitherto been possible. Consider acute Bacillus coli cystitis. One case will clear up within a month and another "hangs fire" indefinitely. It appears as though one had omitted something in the latter case. The filterable phase may have much to do with this, and this suggestion is borne out by the author's experience, namely,

that one cannot get too close to the pathogenic germ if one desires successful results, and incidentally that is why stock vaccines so often fail.

Dr. Hort's work teaches the same lesson, which is often ignored, and yet is, on common-sense grounds, one of obvious deduction. This principle of germ-specificity might be summarized in the words "The virus, the whole virus, and nothing but the virus." Besides the above diseases, typhus and anterio-poliomyelitis have been the subjects of work upon the filterable virus. The latter disease is an important one, even from the Army's point of view.

Diseases: Poliomyelitis, Polio-encephalitis

No less than 67 cases of this disease occurred in Aberdeen in 1916. A few cases occurred in Dublin and Belfast. Norfolk, Suffolk, Staffordshire, and Birmingham have all had small epidemics in recent years, and sporadic cases appear in London from time to time. In France, the disease has been noted since 1909, and although children are usually the victims adults often get the complaint. In 1916 New York had a very severe epidemic, and in view of the many troops now arriving from the American continent one may see more of the disease in the summer of 1918. Wherefore I propose to discuss its ætiology and treatment briefly.

The toxin of this complaint is a filterable virus.

Inoculation of certain apes with emulsions of the cord of a diseased person, under aseptic conditions, reproduces the disease (Landsteiner and Popper) (4).

In 1912 Kling recovered the virus from washings of the mouth, nose, trachea, and small intestine of fatal cases. In 1913, Flexner and Noguchi grew the "globoid bodies" anaërobically on ascitic agar with which they inoculated apes and successfully reproduced the disease. From the nasopharynx of "carriers" and from the gastro-intestinal tract it was possible to extract the organism, which was extremely minute, only 0·2 μ in diameter. It grew in pairs, chains, or masses like Hort's bodies aforementioned. This filter-passing virus does not behave like most ordinary germs. Agglutination and complement-deviation were found to be negative by Amoss—that is to say, it did not show any of the typical reactions of immunity. Notwithstanding, immunity was developed—and strongly too. Even though the attack was thirty years ago, serum of a recovered case will protect a virus-inoculated animal. The virus itself is stable, and will keep in glycerine for at least six years.

It was found that the virus travels centripetally *via* the peripheral nerves—for instance, the optic, nasal, or sciatic. Certain animals, especially the stable-fly or rat-flea, are said to convey it. Quarantine should last at least 14 days. Flexner made the valuable observation that the absorbing areas must be damaged first, *e.g.* the nasal cavity or spinal cord, though the damage need only be incurred by contact with a foreign protein. Intrathecal injection of horse serum was sufficient to damage the cord for such a purpose.

Immunization against Poliomyelitis.—Passive immunity is classically illustrated in this disease. Netter (5), in France, injected intrathecally the serum of a cured patient. Horses cannot be immunized for this purpose. Flexner proved that the serum was efficacious by curing apes who suffer from a severer form of disease than do men. In man there is a prodromal period of 2–4 days. The serum should be given as early as possible in the disease.

Netter's dose is 5–13 c.c. daily for 8 days. His figures (1915) are these :

Cases : 32 treated with serum.

Mortality (average of untreated cases, 5–17% as regards serum).

Mortality of Netter's cases, 25%, but this epidemic was unquestionably a severe one.

Details :

Rapid recovery . . .	6
Nearly complete recovery .	3
Greatly improved . . .	7
Undoubtedly improved . .	5
Not improved	3
Died	8
	32

Robb (6), of Belfast, in 1916 finds that urotropine in its cerebro-spinal antiseptic action will modify the disease—that is, produce a milder form.

Flexner (7), in 1916–17, having the experiences

of the large epidemic of poliomyelitis in New York to draw upon, recommends the combination of intravenous and intrathecal injection of immune serum. For a child of 2 he advises 5–10 c.c. intraspinally plus 30–40 c.c. intravenously. In children intravenous injection is difficult, as any one who has tried it knows. Subcutaneous injection was generally resorted to in New York. The immune serum was collected from convalescent patients aseptically, tested for sterility, and used without inactivation or the addition of disinfectants. The possibility of conveying the infecting virus is not esteemed a danger, because the virus has never been detected in human blood, and even if it were present in small amounts it would be neutralized by the amount of immune bodies in the serum. In any case of tapping the spinal theca, followed by injection of serum, the "purulent aseptic effusion" of Widal may appear. The fluid subsequently drawn off is found to be sterile, but turbid and depositing a clouse of polymorphonuclear leucocytes. This "serous meningitis" need give rise to no anxiety.

The further study of poliomyelitis will undoubtedly throw light upon such diseases as tetanus, cerebro-spinal fever, and possibly upon cerebro-spinal syphilis.

Disease: **Rabies or Hydrophobia**

This disease is another example of a filterable virus. It hardly comes within the purview of

military medicine, and is fully dealt with in standard works.

For the benefit of the civilian practitioner, however, it will be well to tabulate a few facts for reference in case of emergency.

Ætiology.—Negri, in 1903, described certain bodies in the ganglion cells of the central nervous system which are specific for rabies. They are probably protozoal. The virus is most definitely filterable and can be subcultured, as Noguchi has shown. It was Pasteur, in 1880, who attenuated the primary virus (*street virus*) and produced successful *prophylactic* immunity. If the virus is a protozoon, this fact should throw much light on other protozoal diseases, such as syphilis.

The virus is contained in the saliva of the rabid animal. Wolf-bites are far more deadly than are dog-bites. Scratches suffice to infect, but not all bites from rabid dogs engender rabies. As in tetanus, the virus travels up the neurons to the central nervous system.

Incubation Period varies from 9–60 days, according to the (*a*) site of injury, (*b*) dose of poison, (*c*) kind of animal.

Bites on the face or the fingers are very dangerous. 16% of untreated cases of rabid dog-bite contract rabies. Only 0·46% of Pasteur-treated cases develop the disease.

Management of Cases.—(1) Destroy the rabid animal. Cut off its head and send this or

the carcase in ice or glycerine to the appropriate laboratory for pathological examination.

(2) If the animal is obviously rabid, proceed *instanter* with treatment. Do not wait for the report.

(3) If not, cage it; and if it becomes rabid, proceed as above.

(4) Destroy any other animals the rabid animal has bitten.

(5) Cauterize all bites with pure carbolic acid.

(6) Mr. Walter Long's Muzzling Order did great good in keeping down rabies in England. The Americans acknowledged this.

The Vaccine.—By passing the virus through a series of rabbits, the period of incubation is variously abbreviated to a minimum of 6–7 days. Its toxicity is also diminished (*virus fixé*). Drying the virus further attenuates it. Emulsions of desiccated cords of these animals are therefore injected aseptically.

Administration.—There is no need to vary the dose according to age (as with diphtheria antitoxin). There may be a slight local reaction. Cases of *severe* injury about the face or fingers require the *intensive treatment*; others only the *mild* treatment. The uniform dose is 2·5 c.c. of cord emulsion.

Wolf-bites being more deadly should be treated intensively. The mortality of such when treated is 10% (intensive) and untreated 40–60%.

Once rabies has set in, specific therapy is unavailing. Anti-rabic sera are useless, so far.

SCHEDULE OF TREATMENT (KOLMER)

Day.	Mild treatment.	Intensive treatment.
I .	14 and 13 day cord	12 and 11 day cord (twice)
II .	12 ,, 11 ,, ,,	10 ,, 9 ,, ,, 8 and 7 day cord, p.m.
III .	10 ,, 9 ,, ,,	6 day cord.
IV .	8 ,, 7 ,, ,,	5 ,, ,,
V .	6 day cord	4 ,, ,,
VI .	5 ,, ,,	3 ,, ,,
VII .	4 ,, ,,	2 ,, ,,
VIII .	3 ,, ,,	4 ,, ,,
IX .	2 ,, ,,	4 ,, ,,
X .	4 ,, ,,	1 ,, ,,
XI .	3 ,, ,,	4 ,, ,,
XII .	2 ,, ,,	3 ,, ,,
XIII .	4 ,, ,,	2 ,, ,,
XIV .	5 ,, ,,	4 ,, ,,
XV .	2 ,, ,,	1 ,, ,,
XVI .	4 ,, ,,	4 ,, ,,
XVII .	3 ,, ,,	3 ,, ,,
XVIII .	2 ,, ,,	2 ,, ,,
XIX .	4 ,, ,,	4 ,, ,,
XX .	3 ,, ,,	3 ,, ,,
XXI .	2 ,, ,,	2 ,, ,,

The mortality of rabid dog-bite cases is :

Untreated, in all . 16%

Treated :

Face bites . .	1·25%	Average 0·46%
Hand bites . .	0·75%	
Bites elsewhere .	0·25–1%	

Rabic vaccine is essentially a prophylactic vaccine, nothing more. It is best where possible to send the patient to a Pasteur Institute for treatment.

CHAPTER III

CEREBRO-SPINAL MENINGITIS

Ætiology.—Still (1), in 1898, identified the coccus of basal meningitis of children, which is only a variation of the meningococcus of Weichselbaum discovered eleven years later, and commonly identified as the causative organism of cerebro-spinal fever. The organism in question has had a very hard struggle to maintain an independent existence. It is only confusing from the practical point of view to consider the many permutations and combinations which the varieties of the meningococcus have undergone in time past. This phenomenon of type variation is but a marked form of that germ-specificity which is of such practical importance in vaccine work. With vaccines the precise organism must be used in the vaccine to secure good results. With sera, although more latitude is permissible, the type must also be adhered to. Colonel Mervyn Gordon, in charge of the Central C.S.F. Laboratory, has done most valuable work upon the elucidation of the meningococcal types. So far as the Army is concerned, he distinguishes four primary types. Types I, II, III, and IV.

Previous to 1914, the state of our knowledge of this matter was as follows :

(1) We knew that the organism of basal meningitis of infants and that of cerebro-spinal fever were one and the same coccus.
(2) We knew that there were sub-groups of the meningococcus, differentiated by the bacterial test of " absorption of agglutinins."
(3) We knew that where we could not identify pharyngeal cocci by this test there might be other types, provisionally classified as " pseudo-meningococci."

Gordon's work advanced (2). He distinguished the four " epidemic types " and found Type II contained three sub-groups. He also showed that the same organism existed in the pharynx as was found in the spinal fluid of cases. " Carriers " were identified as regards the types of germs they carried, and, what was most important from the practical point of view, the dangerous types of carriers could thus be isolated.

Andrewes (3) thinks that the cocci of basal meningitis are distinct from the four types of Gordon, since they are found not to agglutinate with sera derived through such types.

An independent investigation undertaken by the Local Government Board (4) recognized two types only. Gordon's Types I and III, they found, were brought down by the same serum, and only differed in degree as regards agglutination. The same held

good with regard to Types II and IV. The first group, which they called Group I, fermented maltose, and the second (Group II) fermented glucose. Besides which they distinguished the parameningococcus of Dopter. Andrewes (5) believes that ordinarily the meningococci are of low virulence and can only attack the weakest members of the population, which they do in causing basal meningitis of infants. This disease may become epidemic, and then the virulence of the cocci increases. The epidemic strains of cocci stand out with relative but not absolute distinction. Gordon's classification, Andrewes thinks, is good for epidemic work, but to claim his four types as the *only* species of meningococci extant goes too far, in this observer's opinion.

In 1917, Kennedy and Worster-Drought (6) examined 23 cases in the light of Gordon's classification.

Of 8 cases of Type I, 6 died ; all were severe and several " fulminating."

Of 8 cases of Type II, 3 were severe, 4 moderate, and 1 abortive.

Of 6 cases of Type III, (*a*) Those seen early in 1916 were severe or fatal. Instances of hydrocephalus, extreme emaciation, headache, tremor, and torpor were noted. (*b*) Later in 1916 the cases were of moderate severity. All recovered save one.

Type IV.—No proved cases were seen. One doubtful case of this type recovered.

In this there is a clear similarity between Types I and III, II and IV respectively, the former being the more dangerous. The meningococcus has certain cultural characters of distinction. Flack (7), who has worked with Gordon, elaborated a valuable medium for growing the germ, namely trypsin-agar, which consists of a $2\frac{1}{2}\%$ proportion of agar jelly in trypsinized broth, to which 5% pea-flour is added. The mixture is sterilized and made neutral to phenolphthalein. The coccus is Gram-negative and grows with fairly large dewdrop-like colonies, which subsequently become opaque and crenated. It is finally identified by appropriate agglutination tests. A positive result with a dilution of serum 1 in 400, or even 200, is sufficient evidence of identification. The coccus is easily killed by cold or by salivary secretion.

The Toxins of the Meningococcus.—This is a vexed question, and the author apologizes for dealing with it at some length, but it has important bearings on other diseases. According to Gordon (8), an endotoxin, that is an intracellular toxin, is the only poison formed by the above germ. Yet Hort (9) and Caulfield filtered infected cerebro-spinal fluid and cultures bacteriologically, and produced a toxin which, injected into monkeys, caused *continued* fever and death.

Another fact bearing on this matter is the common phenomenon that in the cerebro-spinal fluid of many severe cases one often has to hunt for the cocci in pus cells for a long time, and Gordon (10) suggested

that autolysis accounts for this, the cocci disintegrating and leaving their toxins behind in such cases. The question of an endotoxin is not quite settled. Cocci dried at 37° C. and then mixed with saline solution are as fatal to mice as live cocci. Gordon holds that the toxicity of the bacterial filtrate is explained by autolysis of the cocci with liberation of toxin. On the other hand Hort concludes that the pathogenicity of the cerebro-spinal fluid varies *inversely* as its meningococcal content. Thus far autolysis or a filterable virus afford equally cogent explanations of the often-noted scarcity of cocci in the pus.

Further, Hort (11) finds that the filterable virus produces *continued* fever and death in monkeys. We are then told that this filterable virus is living, cultivable, and can be passed through monkeys. Certainly autolysed cocci cannot be either living or cultivable. Hort goes further and believes that none of the pathogenic results in C.S.F. * are due to the meningococcus or to a toxin. Its pathogenicity is due to the accompanying virus, and in monkeys the pathological changes include gross cerebral changes.

We are here up against diametrically opposite views. In view of the extra weight lent by Professor Adami (12) to Hort's conclusions, it will be well to shortly review the latter's experimental work and report upon it. Rigid controls were observed. The average daily temperature of 150 monkeys was

* C.S.F. = cerebro-spinal fever.

noted, for example. Results certainly show that the mortality varied inversely as the number of meningococci. Moreover, Hort points out that such germs as the meningobacillus, diplococcus of Jaeger, and other cocci are found in the cerebro-spinal fluid fairly often, along with the meningococcus. Again, Flexner certainly killed animals, but only by injecting colossal doses of meningococci intrathecally, so this proves little, and certainly does not clarify the ætiology of this disease.

Adami points out that :

(1) The cultures of the meningococcus obtained from the cerebro-spinal fluid of patients do not reproduce the disease.
(2) That the filterable virus sets up in monkeys fever lasting weeks, and therefore the virus is living.
(3) That this virus is cultivable like the filterable virus of cattle-pneumonia.

Professor Adami can detect no flaw in Hort's technique. *Hort believes the filterable virus and coccus are two phases in the life history of the same organism.* In a recent paper, Gordon (13) dried cocci and extracted a toxin as potent as the cocci. He did not inject dried cocci.

The question is not merely academic, though involved. It bears on the matter of immunity. If Gordon's view of an endotoxin as the only toxin is correct, a vaccine should be prepared, but he uses sera. Now Taylor (14), in 1917, showed that, when

the serum of a patient agglutinated the coccus up to even 1 in 320 parts, the cerebro-spinal *fluid did not agglutinate it*. This also occurs in typhoid. He concludes that bacterial antibodies do not pass over in any quantity to the cerebro-spinal fluid, and therefore vaccines are useless.

Practical experience bears this out. Sera, especially Gordon's, are useful, however. This points by analogy to an exotoxin, though it does not preclude the existence of an endotoxin. Hort's filterable virus is very similar to an exotoxin, but on the other hand is living.

Nevertheless, we must assume that the serum combats this virus-toxin, and so we cannot be far out in assigning to it the functions of an exotoxin.

A recent paper by Gordon states that some of the sera fail to show an appreciable amount of anti-endotoxin for one or other of Types I and II cocci. May not this be explained on the theory that the endotoxin is insignificant compared with the exotoxin or filterable virus ?

It is the author's hope not to have befogged the reader. The subject is somewhat chaotic, but can be summarized thus.

The meningococcus and its pleomorph the filterable virus of Hort is responsible for the disease. The latter might be described as a living exotoxin, for which sera, preferably Gordon's four types, constitute therapeutic antidotes in all cases where positive agglutination confirms the diagnosis.

There are probably other types of cocci, *e.g.* that

of basal meningitis. We can thus distinguish the meningococcus, the infective agent, with intrinsically a relatively weak endotoxin and extrinsically a very potent exotoxin, which is possibly a pleomorphic form, the living filterable virus of Hort.

Prophylaxis.—This is best considered first of all from the pathological side. The route of entry of the meningococcus is apparently a double one. It lodges in the nasal mucus. From thence there is a path *via* certain nerves, *e.g.* the olfactory, to the cerebro-spinal system. Halliburton (15) has shown that dyes can travel along these paths. Worster-Drought and Kennedy (16) appear to have proved that the blood stream also affords a route. Some cases die of septicæmia before the meninges are invaded. They have recovered the cocci from the cardiac valves in such cases. Cresswell Shearer and H. Warren Crowe (17) have shown that in freshly drawn cerebro-spinal fluid some of the leucocytes are alive, as proved by staining with trypan-blue and observing on the warm stage microscopically. They often retain the meningococcus for a long time, and it exists within them alive. In old laboratory cultures rapid phagocytosis occurs with disintegration of cocci. The same applies to nasal strains of chronic "carriers." In the intermediate stage the leucocytes may retain the cocci alive for so long as 60 hours. These writers hold that *infection is carried by the leucocytes.* Virulent cocci at first cannot be ingested, but the longer they grow in the carrier's nasal mucus the more easily digested they

become. When sufficiently attenuated, they are taken up, conveyed to the meninges, and so set up the disease. Gordon (18) showed that saliva inhibits the growth of the meningococcus, but that nasal mucus does not do so. Even 1 part in 100 of saliva will react in this way. A suspension of 1,000 millions of cocci per c.cm. of broth mixed with an equal amount of saliva is completely inhibitory to the growth of the meningococcus. It is the mixed streptococci of the saliva which neutralize the cocci.

Fildes and Baker (19) swabbed 26 cases amongst others. Subsequently, at periods varying from 4–70 days, these cases all developed cerebro-spinal meningitis. Yet of 185 carriers only 4 developed the disease, according to Flack. The cocci therefore may rapidly pass to the central nervous system, and carriers rarely develop the complaint.

Gordon agrees that the disease is spread by "healthy" carriers. Ordinarily 2% of the population are carriers. Rolleston (20) found 2·7% in 10,852 men examined, but amongst contacts the carrier-rate may rise to 20%. Gordon finds that always there is but one type of coccus, and one only in the nasopharynx at the same time in the same person. Contacts yield the same type as the carrier. Some contacts have atypical types, which Griffiths takes to be the "parameningococci of Dopter."

Armstrong (21) swabbed 10,000 men, including 410 carriers. Tulloch examined 324 of these serologically; 103 were released. None of Armstrong's negatives ever had the disease or passed it on. Only

the dangerous types were isolated. Most carriers lose their cocci in a week or two, but others retain them for months. Dakin and Cohen (22) devised Chloramine-T, and Flack (23) applied this substance to the disinfection of carriers by means of a spray. The air of a chamber was saturated with this disinfectant to such an extent that staphylococci were killed on exposure to it. Chloramine-T vapour is non-toxic to man. Inhalations of 15–20 minutes usually kill the meningococci. Of 14 chronic carriers, all but 3 were cured after 13 inhalations. Other prophylactic measures include disinfection of urine, clothing, bedding, etc. Twice a day insufflation and gargling with potassium permanganate 1 part with 5,000 of normal saline should be adopted.

The atomiser of Flack is used to reduce the carrier-rate where it rises much above the normal 2%. Swabbing is best carried out by means of a West's swab, which protects against salivary contamination.

The disease is protean in its manifestations. Most typically there is intense headache, pain, and stiffness in the neck muscles, with head-retraction, fever, vomiting, delirium, succeeded by coma.

Polyuria is often an early symptom.

Photophobia, strabismus, and Kering's sign are often present.

Statistics.—Cerebro-spinal fever finds an excellent breeding-ground amongst military forces.

Newsholme (24), early in 1915, saw that a severe epidemic was imminent. It attained its maximum in March and April. He noted in 1915 2,566 civil

and 1,146 military cases. In 1913 there were registered but 279 cases. In 1916 about 50% of 1915.

Robb (25), of Belfast, reports the following age mortality figures :

Age.	Cases.	Mortality.
Under 1 year	9	33·3%
1– 2 ,,	3	33·3%
2– 5 ,,	3	0·0%
6–10 ,,	4	25·0%
11–20 ,,	16	12·5%
21–30 ,,	8	25·0%
31–40 ,,	2	50·0%
41–50 ,,	2	100·0%
Over 50 ,,	1	100·0%

Clay (26) reports 51 cases, 37 males and 14 females, in which 29 developed a rash. 77% had a serum rash.

Serum Treatment, with Results.—The Army use Gordon's sera nowadays. There are five sera :

Type I serum (Gordon) monovalent.
,, II ,, ,, ,,
,, III ,, ,, ,,
,, IV ,, ,, ,,
Mixed serum with 40% Type I.
40% ,, II.
10% ,, III.
10% ,, IV.

The last is used until the type of coccus is diagnosed, then the appropriate serum is injected. The serum is given intraspinally under a general anæsthetic. An equal amount of fluid is removed first and 30 c.c. is given daily for four days. The foot

of the bed is raised after the operation. The eyes must be looked after carefully. If a relapse occurs, more is given. If the serum is effective, the cocci are not recoverable from the cerebro-spinal fluid after twenty-four hours, according to Embleton.

Rolleston (27), reporting on naval cases, gives these statistics. In the first year of war the mortality was 52·9%. In 1915–16 it was 35·6%. The mortality rose with age. It was 67·3% up to 20 years and 79·8% up to 25 years of age.

In regard to the early use of serum, as in diphtheria, this is of paramount importance.

Flexner's Cases (America)	Mortality.		Rolleston's (Navy)	Mortality.
Serum given in first 3 days	18%	1,211 cases		29·7% (74 cases)
Given 4th to 7th day	27·3%			33·8% (15 cases)
Given later	36·5%			50% (6 cases)

Gray (London Area)	Mortality.	Robb (Belfast)	Mortality.
Serum given in first 3 days	9·09%	Serum given in first 5 days	22·2%
Later	50·0%	Later	41·6%

Rolleston compares the different sera :

Serum Brand.	Mortality.	Recoveries.
Flexner	22·3%	77·7%
Gordon	18·7%	81·3%
Pasteur Institute	44·5%	55·5%
Burroughs Wellcome	33·3%	66·7%
Mulford	50%	50%
Lister Institute	54·5%	45·5%

From which it will be seen that Gordon's sera are the best and Flexner's next, and of the commercial sera, Burroughs Wellcome's.

Of the serum rashes 23% were erythematous or urticarial. Rolleston has combined hexamine and soamine treatment by mouth with sera, but it does not appear that any special benefit arose from this or from vaccine treatment. It is hoped that the above points may form a concise modern summary of the recent valuable work on cerebro-spinal fever. Undoubtedly, if Gordon's share of it is leonine, Hort's is also brilliant and original.

CHAPTER IV

TETANUS

Ætiology.—Tetanus or "lock-jaw" is a disease with an evil pedigree. It was known in Ancient Greece, and has been a dreaded scourge in all ages. Professor Bulloch (1) described tetanus as a disease in which treatment has not advanced since the days of Hippocrates. This writer points out that even twenty years after the introduction of antitoxin the value of the latter is still a matter for discussion. In regard to the latter contention he is correct, but not in regard to the former. In the Franco-Prussian War tetanus claimed a mortality of between 80 and 90%. Nowadays (1916–17, British Army) the mortality is 50·8%. Yet this is still a heavy mortality. Even to-day at least one man in 1,000 in home hospitals gets tetanus (2), so that this remains a matter for our most earnest consideration. Very large sums of money are being spent by the Government on tetanus antitoxin. No sum is too great to spend upon such a worthy object.

Now it is a curious fact that whereas there exists abundance of experimental evidence concerning all features of tetanus as regards prophylaxis, yet when

one looks for direct evidence of the curative value of antitoxin in developed tetanus the evidence is far to seek. The fact is *it does not exist.* If you give an animal the minimal lethal dose of tetanus toxin and wait for the toxin to become affixed to the nervous tissues, no amount of antitoxin in this world will cure that animal.

This is borne out by the fact that in order to immunize animals—for instance, the horse—against tetanus you must inject *both toxin and antitoxin together* at first and for several times before giving toxin alone, since if once fixation of toxin to nervous system occurs the animal is doomed. It will therefore be seen that the War Office were eminently right in prescribing preventive doses of tetanus antitoxin for every wounded man, for its universal application is based on the cardinal fact that *tetanus toxin, if introduced into any animal which has not free antitoxin in its blood, is almost invariably fatal.* And if the amount of toxin introduced is not sufficient to kill in the absence of antitoxin, then indeed antitoxin cannot be claimed to cure such cases.

The above unsystematic beginning of the chapter is so placed because the author wishes the rest of the chapter to be read in the light of such remarks. He ventures to think they may explain a few of the current perplexities which surround the problem of tetanus and its cure.

Prophylaxis.—Untreated tetanus gets well in some instances. The actual percentage of spontaneous

cures depends largely on the surrounding conditions. In the Franco-Prussian War, Richter (3) found the total mortality to be between 80 and 90%. Bruce (4) quotes 8 cases of tetanus following trench feet in this war. None of these had A.T.S.* Two only out of 8 survived, *i.e.* a mortality of 75%. The difference between this and Richter's figures allows 5–15% for improved surgical conditions. Let us consider Richter's figures in regard to incubation period and mortality.

Incubation period.	Cases.	Mortality.
1–7 days . . .	87 (28%)	96·5%
8–14 ,, . . .	99 (43%)	85·5%
15–21 ,, . . .	29 (13%)	55%
Over 21 days . .	13 (5·7%)	Not given.

The above figures prove that in pre-serum days

(*a*) The most fatal cases were those with short incubation periods;

(*b*) That 8–14 days is the commonest incubation period;

(*c*) That the longer the incubation period, the higher the percentage of recoveries.

Golla gives other statistics to prove this. We can compare the above with these figures (Golla) of 1,914 cases which had no prophylactic serum:

Incubation period.	Cases.	Mortality.
1–7 days . . .	17 (32·7%)	82·5%
8–14 ,, . . .	24 (46·2%)	79·0%
15–21 ,, . . .	6 (11·5%)	54·0%
Over 21 days . .	5 (9·6%)	Not given.

* A.T.S. = anti-tetanic serum.

We see that (*a*), (*b*), and (*c*) still held good for 1914, as they did for 1871. A reduction of 15% is allowed for better surgical conditions.

Since prophylactic doses of A.T.S. were introduced, tetanus has developed two modifications. There are, therefore, three modern types:

I. Tetanus with initial trismus (like the old type).
II. Delayed tetanus } Modified tetanus.
III. Local tetanus }

I

Now let us consider **the cases with initial trismus** which had prophylactic doses (5).

Incubation period.	Cases.	Mortality.
1– 7 days . . .	61 (22·6%)	75·5%
8–14 ,, . . .	93 (34·6%)	70·0%
15–21 ,, . . .	33 (12·2%)	60·8%
21–30 ,, . . .	19 (7·05%)	62·8%
30–40 ,, . . .	14 (5·2%)	57·0%
40–50 ,, . . .	9 (3·3%)	33·4%
50–60 ,, . . .	18 (6·7%)	27·7%
Over 60 days . .	22 (8·2%)	40·8%

The mortality, on the whole, drops with the lengthening incubation period, although there is a rise of mortality in the very late cases. Here again 8–14 days is the commonest incubation period. Thus, *even in the worst type of case, mortality has dropped 7% since the introduction of serum.* Comparing the 1914 cases with these, the reader should note that in the former no less than 78·9% were manifest within the first fortnight. Since prophylactic serum

was used only 57·2% are evident within the first two weeks. This definitely proves that the incubation period is lengthened by A.T.S., even in the severest cases. The mortality of such cases is also lower.

II

Consider now the cases of "**delayed tetanus**" (6).

Incubation period.	Cases.	Mortality.
1– 7 days . . .	23 (16·5%)	82·5%
8–14 ,, . . .	25 (18·1%)	76·0%
15–21 ,, . . .	16 (11·5%)	50·0%
Over 21 days . .	74 (53·5%)	20·2%

Here we see that the largest number of cases had the *longest* incubation period and the *lowest* death-rate.

III

Thirdly, consider **local tetanus** (7).

Incubation period.	Cases.	Mortality.
1– 7 days . . .	13 (10·9%)	Nil
8–14 ,, . . .	18 (15·2%)	Nil
15–21 ,, . . .	31 (26·1%)	Nil
Over 21 days . .	57 (48·8%)	Nil

Here, again, the majority of cases have the longest incubation period. *There is no death-rate from these cases.*

Combining I, II, and III, we get—

Incubation period.	Cases.	Mortality.
1– 7 days . . .	97 (18·2%)	67·0%
8–14 ,, . . .	136 (25·8%)	61·5%
15–21 ,, . . .	80 (15·5%)	35·0%
Over 21 days . .	213 (40·5%)	24·3%

which table unquestionably proves that prophylactic A.T.S. lengthens the incubation period and lowers the death-rate proportionally to such lengthening.

The value of prophylaxis in tetanus may be considered firmly established therefore. There is also evidence that in 10 days such immunity is largely lost. Many cases of tetanus have occurred in healed wounds or practically clean wounds. The War Office consider that all wounded men shall have at least 4 doses of serum, at intervals of 7 days. Trench-feet cases even *without* obvious breach of surface are to be treated similarly.

The dosage in such cases is 500 U.S.A. units. The U.S.A. unit was defined by the pioneers of A.T.S.—namely, Rosenau and Anderson (8)—as "*ten times the least amount of serum necessary to save the life of a 350-gramme guinea-pig for 96 hours against the official test dose of a standard toxin.*"

The test dose consists of 100 minimal lethal doses of a precipitated and dried toxin, tested out against 350-gramme pigs and preserved at a central institution.

No. of pig.	Weight in grammes.	Subcutaneous injection of a mixture of		Time of death.
		TOXIN (test dose).	ANTITOXIN (strength unknown).	
		Gramme.	c.c.	
1	360	0·0006	0·001	2 days, 4 hours.
2	350	,,	0·00125	4 ,, 1 hour.
3	350	,,	0·002	Symptoms.
4	360	,,	0·0025	Slight symptoms
5	350	,,	0·003	No symptoms.

The standardization is simple and interesting, and is illustrated by the preceding table :

No. 2 is the nearest. This amount of serum, therefore, represents $\frac{1}{10}$th of 1 unit.

The primary injections at the Front consist of 500 units U.S.A. The subsequent injections are similar. The serum is preserved with tricresol 0·4% or phenol 0·5%.

Previous to any surgical interference with a wound at least 500 units should be given, preferably 48 hours before the operation. This is vitally important. Almost every one of the cases I have seen in home hospitals was post-operative. In one case a man had two operations and moderately severe tetanus after both. The surgeon has a grave responsibility in this matter. It takes 48 hours for a subcutaneous injection to be absorbed.

Certain antiseptics are helpful in the prevention of tetanus which also neutralize toxin. Such are the oxidizing antiseptics hydrogen peroxide, permanganate of potash, chlorine water, Dakin's solution, and iodine.

One school of thought teaches that to sow the wound with a certain sporing anaërobe, morphologically not unlike tetanus—namely, the Reading bacillus (B. sporogenes)—is of therapeutic value, and excellent results are claimed. Mayo Robson (9) endorses this teaching. With all due respect, I submit, on pathological grounds, especially in view of the fact that tetanus is often unrecognizable in cultures for weeks (10), that this practice incurs a

grave danger of inadvertently introducing tetanus germs. Even if these cultures be tested upon animals with negative results, the danger still remains, for some animals, *e.g.* mice, one has known to survive injections of true tetanus bacilli occasionally. The treatment may be excellent, but its risks are to my mind of the first magnitude.

The Toxins of Tetanus and their Route of Entry and Passage.—Of all germs none produces greater toxicity than the tetanus bacillus. The number of organisms producing sufficient toxin to cause a fatal infection is so small that careful anaërobic cultures from the local lesion may fail to reveal the presence of tetanus bacilli. According to Ehrlich, tetanus toxin is composed of two separate and distinct substances :

(*a*) *Tetanospasmin*, a neurotoxin which is very unstable and responsible for the severe symptoms;
(*b*) *Tetanolysin*, a hæmolysin, more stable.

The former is very susceptible to heat, age, and even light, but can be precipitated by ammonium sulphate and kept in a dried state as yellow, crystalline masses. Tetanospasmin affects motor nerve-cells ; result chronic convulsions, rigidity, and irritability.

Tetanus furnishes an excellent example of an exotoxin. The bacilli and spores do not usually enter the blood, but may occasionally. Burrows (11) recently reported a case of infarct of the lung accom-

panied by tetanus of the neck and shoulder and respiratory muscles where the original wounds were in the arm and legs (splanchnic tetanus). The blood of a patient with tetanus contains toxin. Neisser produced tetanus in mice by injecting such blood. Tetanospasmin has a strong affinity for nervous tissue. Symes (12), agreeing with Meyer and Ransom, has shown that the toxin passes up the motor nerves by the fibres rather than by the lymphatics, as was formerly believed. *Nerves should therefore be infiltrated with antitoxin as soon as possible after the injury has been received, where possible.*

It is doubtless through the end-plates of the motor nerves that the toxin gains access to the neurons, passing up to the central nervous system. The poison reaches the spinal motor ganglia on the side inoculated; it then affects the ganglia on the opposite side, reducing their insulation and making them irritable, the result of which is spasticity of the muscles supplied from them. The toxin next affects the sensory apparatus and the reflexes increase. Eventually spasm of all striated muscle and generally reflex tetanus obtains.

There is always an incubation period, fortunately. Antitoxin in sufficient amount will neutralize the toxin as quickly as it is produced, and thus protect until the bacilli and spores are destroyed by the mechanisms of natural immunity.

The Action of A.T.S.—Antitoxin will neutralize toxin if free, *not otherwise.* Nevertheless in developed tetanus antitoxin should be given at once

and in large amount and by the quickest (intrathecal) route, *as this prevents any additional fixation of toxin to nerve.* There may be some loosely-combined toxin which A.T.S. may tear apart and neutralize, but this has not been proved; also no doubt it contains antibodies which aid the corporeal mechanisms of immunity.

Sherrington (13), experimenting upon monkeys, was able to save the life of a larger number of animals which had received lethal doses of toxin by administering A.T.S. by the intrathecal route than by any other. His figures are these:

TWENTY-FIVE CASES OF MONKEYS

Route of injection.	Time between giving of Toxin and Antitoxin.	Recoveries.	Deaths.
Lumbar intrathecal . .	47–78 hours	14	11
Bulbar intrathecal . .	,,	13	12
Intravenous . . .	,,	7	18
Intramuscular . . .	,,	3	22
Subcutaneous . . .	,,	2	23
Cerebral subdural (10 cases)	,,	0	10

Irons (14), on the other hand, treated 16 acute cases by the lumbar intrathecal method, and 81·2% died. Of 11 cases treated intravenously 72% only died. The case for intrathecal injection is not, therefore, incontestable. Anaphylaxis is more likely, however, with intravenous injections.

Ransom (15) and others hold that antitoxin never reaches the nerve-cells, but Sherrington's experiments do seem to show that toxin which is only partially united can be detached by a sufficient concentration

of antitoxin in the surrounding lymph spaces. Sherrington never waited longer than 78 hours between the injections of toxin and antitoxin, since he knew that once tetanus was properly developed antitoxin could do little if anything in the matter of a cure.

The Forms of Tetanus

I. *Tetanus with Initial Trismus.*—Amongst the early symptoms one may find anxiety, pains in the back and neck, restlessness, outbursts of unreasonable temper, insomnia, headache, yawning, dysphagia, excessive sweating, and difficulty of micturition. Salaman (16) has noted a new sign, *i.e.* loss of the swinging movements of the jaw.

II. *Delayed Tetanus.*—In this form we get local spasticity persisting for weeks or months, which may or may not develop into generalized tetanus.

III. *Local Tetanus.*—This form is confined to local rigidity of the muscles around the wound, accompanied often by pain. It lasts for a varying time.

IV. *Splanchnic Tetanus.*—Follows usually wounds of chest or abdomen, and rarely limb wounds. A typical example has been described above.

I, II, and IV are often fatal, not so III.

The Treatment of Tetanus.—In military work this becomes a systematic business. A committee of medical officers drew up the following rules, which apply to this hospital (B.R.C.H., Netley), and which constitute a convenient summary for general use.

(1) Each wounded patient will be supplied with a tetanus card on admission, of which this is a copy :

ANTI-TETANIC INJECTIONS

Name: Smith, John. Admitted, 1.1.18.
Ward, 23. When Wounded, 20.12.17.
Admission Number, R.49.
Injections before Admission—Dates, 20.12.17. 500 units.

ANTITOXIN

Issued.	Injected.	Remarks.
2 Jan. 1918.	2.1.18, A.B.C.	B.W. & Co. 509
9 Jan. 1918.	9.1.18, A.B.C.	L.I. 105 F. Urticaria, 22.1.18.

(2) All data referring to injections of anti-tetanic serum and to the symptoms and treatment of attacks of tetanus will be entered on this card.

(3) *Prophylaxis of Tetanus.*—Each patient with a septic inflammation of tissues will receive a subcutaneous injection of 500 units of serum within 48 hours of admission.

(4) In cases where the wound remains septic, further injections will be given at intervals of seven days.

(5) When an injection is to be given, the tetanus card will be sent to the Pathological Laboratory, where the dose will be issued and the card stamped with the date. After the injection the M.O. in charge of the case will initial and enter the date in the space provided. He will also record briefly any untoward symptoms, such as urticaria, which may follow the injection.

(6) The M.O. in charge of the case will decide when further injections are unnecessary and will enter the reason briefly on the card.

(7) *Occurrence of Tetanus.*—In the event of tetanus supervening an intramuscular injection of 5,000 units of serum must be administered immediately, and the case reported without delay to the senior M.O. and to the pathologist. A syringe and a supply of serum are kept for emergency use in the room of the O.M.O. (Orderly Medical Officer).

(8) All Nursing Sisters engaged in dressing wounds should report at once to the M.O. if the muscles round the wound are harder or more rigid than usual.

Developed Tetanus

Acute General Tetanus.—The more acute the case, the larger the dose necessary. When lumbar puncture is done, an anæsthetic should be given and 20 c.cm. of cerebro-spinal fluid drawn off. High potency serum (800 units per c.c.), of which 16,000 units are contained in 20 c.c., is injected very slowly, and should be supplemented if necessary by 8,000 units intramuscularly. The amount for an acute case should be roughly as follows:

Day.	Subcutaneous. Units.	Intramuscular. Units.	Intrathecal. Units.
1st day . .	—	8,000	16,000
2nd ,, . .	—	8,000	16,000
3rd ,, . .	—	4,000	8,000
4th ,, . .	—	4,000	8,000
5th ,, . .	2,000	—	—
7th ,, . .	2,000	—	—
9th ,, . .	2,000	—	—

On the second day the " purulent aseptic effusion " of Widal may be noticed in the cerebro-spinal fluid

drawn off. No cause for alarm exists by reason of the appearance of this "serous meningitis."

Drug Treatment.—H. S. Souttar reports excellent results from the use of large doses of chloretone per rectum (grs. xxx in olive oil, ℥iv). This drug is non-toxic. This worker believes that, if only the spasms can be abolished, the disease tends to cure itself spontaneously. Other sedatives commonly used are morphia, gr. ¼ every 4 hours, chloral hydrate, potassium bromide or paraldehyde (grs. xx *aa.* 4 hourly), combined with Tr. digitalis ♏x. Carbolic acid has no influence upon the disease. Magnesium sulphate may ease the spasms temporarily if injected intrathecally, but is dangerous.

In the author's opinion, treatment must depend upon the severity of the case. It is by no means certain that large doses of antitoxin may not sometimes cause severe collapse; but in view of the nature of the disease both sedatives and antitoxin should be employed, the latter invariably, but *with discretion* as to the amount. The neutralization of free toxin may make all the difference between life and death. *Time is therefore essentially a vital factor.* Not a moment must be lost in giving antitoxin, once the case is thought likely to be tetanus.

The Surgical Treatment of the Wound during Tetanus.—Animal experiments show that amputation is of no avail in cutting short the attack. It is safer to leave the wound alone as regards gross interference until tetanus has subsided. Oxidizing antiseptics should, however, be used in dressing the wound.

CHAPTER V

Part I

DIPHTHERIA ANTITOXIN—ANTI-STREPTOCOCCUS SERUM —SERUM IN PNEUMOCOCCAL INFECTIONS—GAS-GANGRENE ANTITOXIN—ANTI-PLAGUE SERUM—ANTIVENIN AND ANTI-SCORPION SERUM—COLEY'S FLUID—ANTI-BOTULISMUS SERUM

In this chapter our review of sera will be completed.

Serum in Diphtheria

Toxins and Antitoxins.—The toxin of diphtheria consists of three parts:

(1) A general neuro-muscular toxin (Ehrlich's "toxone");
(2) A toxin producing local œdema (Ehrlich's "toxoid");
(3) A toxin producing paralysis (Ehrlich's "prototoxoid").

The first has the greatest affinity for antitoxin, the second less, and the third least. That is why paralysis is so common. Diphtheria bacilli vary

considerably in regard to the quantity of toxin they secrete. The toxin is essentially an exotoxin. The washed germs, if injected, are atoxic or only slightly poisonous. The toxin, acting locally, produces necrosis of surface epithelium, which together with fibrin and leucocytes constitutes the "membrane." The toxin is absorbed, and, as in tetanus, the bacilli rarely appear in the blood or organs. Later, the third constituent comes into play and paralyses certain motor nerves and ganglia, especially those of the heart and palate.

The virulence of diphtheria bacilli *cannot* be inferred from their morphological appearance. An animal must be tested. In doing this a few essential precautions must be taken.

(1) The culture must be pure.
(2) If good growth on bouillon does not occur, transplant until the germ has been "educated" to grow well. Grow for 3 days at 37° C.
(3) Select a 250–300 gramme guinea-pig and inject aseptically 2 c.c. in the median line with *unfiltered* culture.
(4) Observe the animal for 4 days. *Even slight toxæmia indicates a positive result*, especially if there is local œdema.
(5) If no symptoms occur, *wait for paralysis in two or three weeks.* The test is not theoretically negative unless this fails to occur.
(6) Into another pig inject 500 units of the anti-

toxin + 2 c.c. of culture mixed beforehand and incubated for an hour at 37° C. It should not die.

When an outbreak of a mild character occurs, it is as well to have the above animal test performed. In regard to "carriers" who may harbour germs indefinitely in their throats, the animal test is of value in that an apparently healthy carrier may harbour virulent germs.

The discovery of diphtheria antitoxin and its use in the treatment of this infection constitute one of the triumphs of modern medicine. Twenty years ago the mortality was 30% ordinarily, but laryngeal diphtheria was appallingly fatal. An old teacher of mine at one of the London fever hospitals told me that before the introduction of diphtheria antitoxin he lost one or more of his hospital staff *per annum* through diphtheria. Since using antitoxin he has lost not one from diphtheria.

Behring first used diphtheria antitoxin therapeutically. The *antitoxic unit* is "the smallest amount of serum that will neutralize 100 times the minimal lethal dose for a 250-gramme guinea-pig."

Horses, previously tested against tubercle and glanders by means of tuberculin and mallein, are immunized by gradually increased doses of toxin and then bled aseptically and the serum separated, standardized as in tetanus, and a small amount of antiseptic added.

The figures which prove the value of diphtheria antitoxin can be found in most text-books on immunity. Here are the Metropolitan Asylums Board figures, concisely:

PRE-ANTITOXIN DAYS

	Mortality average.
1888–1893	33%

FIRST YEAR OF ANTITOXIN

	Mortality.
1894	29·29%

SUBSEQUENT YEARS

	Mortality.
1895–1901	16%
1902–1907	9·5%
1908–1913	7·9%

We thus see that as technique improves the mortality drops.

Dosage.—McCombie (1) gives these doses:

Mild cases . .	4,000–8,000 units in one dose.
Moderate cases .	12,000–16,000 units in one or two doses.
Severe cases . .	20,000–50,000 or more units in two or three doses.
Laryngeal cases .	16,000–24,000 as initial dose, and repeat once or twice, according to persistence of symptoms.

Repeated doses are given within the 24 hours. In fulminant cases a second dose should be given at the end of 12 hours. Severity of the attack is the only basis for dosage. Children often require

more than adults. In the latter delay may be safe, *never in the former.* The antitoxin begins to show its effects in about 36 hours. Its action may be summarized :

(1) It diminishes faucial swelling and distress.
(2) It lessens and arrests nasal discharge and fœtor.
(3) It limits the spread of membrane and hastens its separation.
(4) It improves the general condition.
(5) It prolongs life in fatal cases.

The deadly post-scarlatinal diphtheria used to claim many lives. Nowadays a death from it is almost unknown. There are some important points in regard to the so-called drawbacks of antitoxin. About 20% of the cases get "serum sickness," but in five years McCombie had only two cases of severe anaphylaxis. The actual time of onset is usually 7–10–14 days, but may be within a few hours or as late as 21 days. The earlier the symptoms appear, the worse they are. The symptoms have been described under "Anaphylaxis." In very painful arthritic cases opium is a great relief, and the only thing which appears to be effective. The degree of serum sickness is directly proportional to the *bulk* of the serum given—hence concentration is indicated.

The Limitations of Antitoxin.—All cases will not be saved, but if the serum is given early enough death will be very rare. It must not be forgotten

that the longer antitoxin is delayed, the higher is the death-rate. In any suspected cases *never* wait for bacteriological diagnosis, but give antitoxin at once. There has been an apparent increase of post-diphtheritic paralysis since antitoxin was introduced. This is only because many severe cases have been saved which would otherwise have died, and also because antitoxin does not easily attack the prototoxoid moiety (see above). Albuminuria is commoner. The mere fact of introducing pure albumen may account for this; possibly also the rapid excretion of semi-neutralized toxin has something to do with it. Asthmatics are prone to severe anaphylaxis with this serum.

Contacts.—Throats should be examined daily, and at the first sign of diphtheria give 6,000–12,000 units

Anti-streptococcal Serum

This has been dealt with in Chapter VII, Section I, under Erysipelas. The serum has been in use for twenty years, but its true value is still not affixed. It certainly will do no harm and often does good. It is particularly useful in severe **cellulitis**, also in **septicæmia** (30 c.c. per diem for several days is the dose I use). In severe **anginose** or malignant **scarlet fever** large doses of serum made from the Streptococcus scarlatinæ have, on the whole, given good results. *Not all scarlet fever cases are due to secondary streptococcal infection*, however. The true scarlatinal virus, possibly of Hort's filterable type, yields cases severely toxic and prostrated from the

first. Cases which become ill later are likely to be streptococcal and to benefit from this serum. In **puerperal sepsis** and **streptococcal endocarditis** good results are rare, though in a severe, chronic case of the former the author obtained a rapid cure with this serum.

Erysipelas is also a debated question in this connection, but it is rational to use a serum.

Serum in Pneumococcal Infections

Lobar Pneumonia.—At the Hospital of the Rockefeller Institute, New York, under Dr. Rufus Cole, a special study of pneumonia has been in progress for some years. Analysis of 454 cases shows that the pneumococcus, like the meningococcus, can be classed into four types, with the following degrees of incidence:

Type I . . .	33%
,, II . . .	29%, aberrant form, 5%
,, III . . .	13%
,, IV . . .	20%

Similar investigations at the Johns Hopkins Hospital, Baltimore, by Clough (2), including 54 cases seen between February 1915 and September 1916, agree closely with these figures, except that the aberrant Type II cases were numerous.

F. S. Lister (3), in South Africa, finds Type IV to be rife amongst the blacks in the Rand. Lister also describes four other fresh types prevalent in South Africa.

The pneumococci in the mouths of normal folk, Stillman (4) shows to be most commonly Type IV, next Type III. Types I and II are only common in cases which have been in contact with pneumonia cases. Type II aberrant is rarely but occasionally carried. This is borne out by Stillman's figures:

One Hundred and Eighty-four Persons intimately associated with Type I or II Infections

(i) Positive for Types I or II . . .	11%
Negative ,, ,, ,, . . .	89%
(ii) 297 *persons, not contacts.*	
Positives for Types I or II . . .	0·8%
Negatives ,, ,, ,, . . .	99·2%

From the dust of houses inhabited by patients or carriers of Types I and II these types can be recovered. In other houses of non-contacts the predominant pneumococcus is Type IV. Types III, II aberrant are present. Types I and II are very rarely present. Ergo, infection with Types I or II depends on contact, such contact being direct or air-borne. Another important point emphasized by Sutton and Sevier at Baltimore (5) was that a positive blood culture indicated a grave prognosis.

In Type I pneumonia positive hæmoculture cases were 45·8%, and the mortality 41·7%.
In Type IV pneumonia both were 18·2%.

Negative hæmoculture cases did not die unless there was very marked consolidation.

Anti-pneumococcal serum in 11 cases of Type I

prevented hæmic infection, and Bloomfield (6) claims that it also sterilizes the blood when septicæmia has arisen. My own experience of hæmoculture bears out the fact of grave prognosis in the vast majority of cases of septicæmia. Dochez and Avery (7) have found that the pneumococcus throws out a substance which gives a specific precipitation (precipitin reaction) with the serum corresponding to its type. This may or may not be an exotoxin. If it is, serum therapy of pneumonia lies on firm ground. This soluble substance is excreted in the urine, and continuously in cases of delayed resolution. Its amount furnishes an index of the severity of the infection. If in large amount, the case will be fatal. Cases which do not show it rarely die. Cole (8), independently, noted soluble exotoxins which he called "virulin" and "antiphagin," these he isolated from pleural effusions and the blood; these toxins, Cole says, have the power to fix the antibodies of the pneumococcal serum. Hence, in severe cases, excess of serum should be given. This much, moreover, has been established:

(1) Homologous, *i.e.* highly specific sera are necessary.
(2) Only Type I and II sera have been hitherto found consistently effective.
(3) The serum should therefore only be used for these cases.

Agglutination of pneumococci plays a part in the mechanism of immunity in such cases, and is another

means used of identifying the types besides precipitation.

Dochez (9) reports 65 cases treated with Type I serum, with a mortality of 6·6%, a reduction of 18·4% (the ordinary mortality of Type I pneumonia was found to be 25%).

Type II cases treated with serum have a mortality of 25% as compared with 61% formerly.

Serum disease and anaphylactic shock occur occasionally, but asthmatics do not seem particularly susceptible to this serum. As much as 1,100 c.cm. and 350 c.c. were given in some cases.

The initial dose is 20 c.cm. Serum must be given as early as possible.

In pneumonia, besides the exotoxin of general toxæmia, the endotoxin probably produces the local changes. It may be that in Type I the exotoxin effects are dominant, as in Shiga-dysentery, and that in the other types the endotoxin effects dominate, as in Flexner-dysentery. It would, therefore, be well to determine the value of vaccines in Types I, II aberrant, III, and IV cases.

Pneumococcal meningitis and **septicæmia,** also **delayed resolution** and **empyema** cases, if of Type I, should be treated on the same lines.

Anti-gangrene Serum

Recently Major Bull (10), of the U.S.M.C., experimenting in America and England, has demonstrated the possibility of producing a gas-gangrene

antitoxic serum. Care was taken to produce a pure strain of B. Welchii, but it is not stated whether any discrimination between its four types as described by Henry was made. This germ produces acid in culture which may liberate proteolytic ferments. At any rate Major Bull has produced evidence in favour of a definite exotoxin, which must naturally afford a theoretical argument for producing an anti-serum. Bull has obtained such a toxin in 24-hour cultures; when it is injected into animals such as pigeons or guinea-pigs, local œdema and necrosis occur and hæmolysis of red cells also occurs. Partly hæmolysed matter is found to choke the renal tubules. Inoculation of such a toxin evokes antibodies. Filtered cultures yielded a powerful toxin, evidently a true exotoxin, *i.e.* filter-passing. *2 c.cm. will kill a horse*, after producing local lesions. Prolonged incubation, contrary to the case of diphtheria, yielded a less potent toxin. Antitoxin was made by giving a horse 1 c.cm. of toxin. The reaction subsided in four days. The injection was repeated. *In vitro*, it was possible to exactly neutralize toxin by antitoxin, as in diphtheria. After gas-gangrene has been set up experimentally in horses by inoculation with a culture, a suitable dose of antitoxin will inhibit further developments and lead to cure. Preventive inoculation in guinea-pigs will ensure infection miscarrying.

A human case, a boy with gas-gangrene accompanied by severe constitutional effects, was treated with this serum. Injection caused immediate

amelioration. The temperature fell from 105° to 101°, and the pulse, from being uncountable, improved likewise. The local process was checked, and amputation was followed by a speedy return to normal. Bull believes that even in the severest cases so much general and local improvement is gained by the use of his serum, that whereas formerly the patient was too weak to stand operation or got recurrence, that now, if treated with serum, operation could be undertaken without fear of local extension. At the moment, the serum is not available, as sufficient has not yet been produced, but no doubt this state of affairs will rapidly be changed.

The author believes Major Bull to be on sure ground. The profession owes a double debt to this worker; firstly, on the count of his elucidating and simplifying the toxicology of B. Welchii (*vel* perfringens), and secondly for logically projecting his knowledge into the field of rational therapeutics.

Bull's work, moreover, shows the futility of making curative vaccines from B. Welchii, since the only potent factor is an exotoxin. If one may be pardoned for making a suggestion, it is this, namely, that attention to the Type of B. Welchii, adopting Henry's Types I, II, III, and IV, may prove an important factor in assuring success. In pneumonia attention to the type makes all the difference between the success or otherwise of the serum prepared. This probably holds good for B. Welchii also.

Anti-plague Serum

In this disease we are dealing with a potent endotoxin and a potent exotoxin. We must, therefore, combine vaccines with sera. 50–150 c.c. of sera are given as early as possible in the disease. *This holds good as regards time for every serum used therapeutically.* Intravenous or intramuscular injection is employed to ensure rapid assimilation. Injections are continued every 12–24 hours for two or more days until suppuration has been controlled and the disease begins to abate.

Yersin's serum is used, also one made by the Lister Institute. The Plague Commission of India did not report very favourably on the former serum. Vaccine treatment must be combined with it to get the best results—that is, if we follow the inference drawn from the toxicology of the plague bacillus. Castellani (11) has demonstrated the efficacy of prophylactic vaccination in plague.

Antivenin and Anti-scorpion Serum

Cobra venom and other snake-venoms contain a toxin which paralyses the respiratory centres, and also one which is hæmotoxic and irritant, producing local necrosis and hæmolysis. The former is the most dangerous. Scorpion toxin is similar. The toxins are thermolabile. Calmette heats the venom to 70° C. for one hour. This precipitates the irritant moiety without injuring the neurotoxin. He then injects a horse, beginning with 0·01 gram and increasing up to 4 grams. A true antitoxin is produced

which will neutralize the neurotoxin *in vitro*. It does not alleviate local pain or necrosis, of course Large doses are used—50–150 c.c. in severe bites. Rogers recommends 400–800 c.c. in the worst cases.

Coley's Fluid

This has been used in malignant disease. It consists of a mixed vaccine of Streptococcus erysipelatis and of the Bacillus prodigiosus. Coley recommends the injection of such a vaccine in inoperable cases of sarcoma and carcinoma. The theoretical basis is that such a vaccine produces toxins which stimulate reaction and help to kill the growth, and by so much aid the body in its fight against malignant disease. To my mind, there is nothing in Coley's figures which indicates anything further in the way of spontaneous cure other than is to be found in any series of statistics of malignant disease.

Anti-botulismus Serum

Van Ermengem, in 1896, discovered the Bacillus botulinus, an anaërobe which spores and forms gas and is motile. It can be recovered, when epidemic, from meat, ham, tinned fish, lobsters, oysters, and cheese. It grows at ordinary room temperature, and, after an incubation-period of 24–48 hours, it generates a fatal toxin which attacks certain cranial nerves, causing loss of accommodation and light-reflex in the pupil, aphonia, dysphagia, and hypersecretion of nasal and oral mucus, symptoms which can be re-

peated in the guinea-pig by giving it poisoned food by the mouth. The diagnosis can only be made bacteriologically. Polio-encephalitis must be borne in mind.

The Serum.—Wassermann recently immunized horses against botulism. Statistics in regard to man are not available. The serum should be effective by analogy. The disease is very fatal, though rare.

Part II

Special Note on the Deterioration of Sera

McConkey (12) in 1917 drew attention to this important matter.

Diphtheria Antitoxin.—Anderson, the pioneer of diphtheria antitoxin, gives these figures :

Temperature at which the serum is kept.	Yearly deterioration.
70–95° F.	20%
15° C.	10%
5° C.	6%

McConkey's figures are these :

	Loss of potency.
36° C.	37% in 6 months 51% per annum
6° C. (winter) to 16° C. (summer), *i.e.* room temperature	14% in 6 months
In an ice chest	7% ,,

Sera must therefore be kept in the dark and in the cold. Commercial sera sometimes are 20% below stated potency.

McConkey gives extended figures to prove his points.

Miller (13) considers that the time-limit on the labels is usually quite fair, and that full potency is retained up to that date.

Tetanus Antitoxin.—In reply to personal inquiries, Colonel Harvey, of the Vaccine Department of the R.A.M. College, informed me that the serum was sent out with a potency slightly in excess of the amount stated, and that if kept under proper conditions deteriorated but slightly in a year. The actual rate of deterioration is the same as that of diphtheria antitoxin. High potency serum degenerates more rapidly than ordinary serum.

Anti-meningococcal Serum: Anti-streptococcal Serum.—We cannot as yet accurately standardize these sera, but in regard to the former Tulloch (14) has estimated the anti-endotoxic strength. Probably the same holds good as in diphtheria antitoxin.

Anti-dysenteric Serum.—McConkey states that anti-Shiga serum tested by a provisional method retains its potency for at least a year and a half.

Anti-scorpion Serum.—This serum will neutralize scorpion venom for two years with little or no change in strength.

Anti-plague Serum.—Here, again, two years is the limit.

It should be noted that the decline is in the number of units only. Hence a larger dose makes up for this, and serum should not be discarded in the case of A.T.S. and D.A.* There is no loss in toxin neutralizing power, only in unitage.

* D.A. = diphtheria antitoxin.

CHAPTER VI

ANTHRAX IN ANIMALS AND IN MAN

(*a*) In Animals

Prophylactic Vaccination.—In this case, animals have derived great benefit from specific therapy. Although vaccines do not strictly come within our purview in this section, the case of anthrax is of the highest educational value. Elizabeth Fraser, relative to Pasteur, tells how certain of his critics, anxious to humiliate him, arranged that he should demonstrate his anti-anthrax vaccination at a farm. Sixty sheep were placed at his disposal. Twenty-five were to be vaccinated and 25 left alone. Two weeks later, all were to receive lethal doses of anthrax. Pasteur "made no bones" about it—"twenty-five would die and twenty-five would remain well," he said. Ten were controls. Pasteur was much ridiculed. Excitement rose to a great pitch. One animal developed a temperature overnight and caused Pasteur great anxiety. As a matter of fact, 22 were dead in one night, and the remaining 3 expired the following night in the case of the non-

vaccinated sheep. The others all remained well! Pasteur's triumph was great!

Considering the fact that anthrax forms spores which will withstand boiling at 100° C. for five minutes, the difficulty in making a vaccine can be imagined. Here an entirely new line was taken. Pasteur made his vaccine by growing anthrax at 42° C. Under these conditions, spores are not formed, and after 24 days the germs were not lethal to either guinea-pigs, rabbits, or to sheep (*premier vaccin*). Animals inoculated with such a vaccine could then tolerate a 12-day growth (*deuxième vaccin*). After this, a sheep could tolerate live cultures. This was roughly his method of immunization.

Results.—During 1882–93, 3,296,815 sheep were vaccinated with a mortality, within 12 months, of 0·94% (1). Anthrax ordinarily claims a 10% mortality.

(*b*) Anthrax in Man

There are two chief sera—namely, Sclavo's and the Mulford Company's (American)—which are to-day used therapeutically in anthrax. As the Mulford Company point out, by washing the cultures a means has been found of getting over the difficulty which Pasteur surmounted by prolonged cultivation at 42–43° C.—namely, that of sporulation—and that therefore it is now possible to administer intravenously large quantities of extremely virulent organisms, and so to secure a higher potency serum

than was formerly possible. This is no doubt true. I hold no brief for the Mulford Company, but this piece of work is a good one. The question becomes one of great importance when one recollects that of the three forms of anthrax one is invariably fatal. **"Malignant pustule"** we know can get well, but not so inhaled anthrax starting at the bronchus (**Woolsorter's disease**), and occasionally spores from infected animals may be carried to the intestine, where they cause hæmorrhagic lesions (**intestinal anthrax**).

Sclavo treats his cases with serum without local excision of the lesion (pustule). It is safer to excise. All cases of malignant pustule do not get well. One remembers in this connection a laboratory attendant at one of the London hospitals who died of malignant pustule.

As in pneumonia, a septicæmia is invariably fatal if untreated with serum.

During the operation of excision, all infective material should be soaked up to prevent secondary infection, and the wound should be swabbed with pure carbolic acid.

The serum is prepared from horses.

Administration.—As in the case of diphtheria and tetanus, large doses must be given early and preferably intravenously, despite the fact that this route predisposes to anaphylaxis. (See Section II, Chapter I.) Begin with a dose of 80–100 c.c. at least. Usually, a rigor occurs (T = 104°–105° F.), and then the temperature falls below its previous

level. Repeat with 20 c.c. doses every 12 hours until pyrexia ceases. The potent factor of the serum is probably a thermostable opsonin (6).

Sclavo recommends, in a case of malignant pustule, 30–40 c.c. in doses of 10 c.c., repeated if necessary next day.

Results.—Sclavo, omitting excision in malignant pustule, treated 164 cases with his serum, and reduced the mortality in Italy from 24% to 5·3%.

Summary.—Early excision of the malignant pustule, if on the extremities, is usually followed by recovery (2). Woolsorter's disease is rapidly fatal. In the hæmorrhagic intestinal variety the chances of recovery lie midway between the other two instances.

Positive hæmoculture indicates a grave prognosis. Even 200 c.c. is not too much to give in such cases. Daily blood cultures should be made, and injections repeated every 24 hours until the blood is sterile.

Kolmer (3) reports that cases with sterile blood cultures always recover.

In internal anthrax, salvarsan given intravenously has been found useful. In these cases large doses of serum should also be given intravenously.

SECTION III

SPECIFIC THERAPY

CHAPTER I

NOTES ON VACCINE AND SERUM THERAPY RELATIVE TO SPECIAL DISEASES OF WOMEN

Vulvitis.—Inflammation may be gonorrhœal, diphtheritic, or septic; aphthous or actinomycotic.

In regard to the first, the treatment by vaccines in the acute stage is a justifiable line of therapy, and has been dealt with earlier in this book. Bacteriological diphtheria of the vulva should, of course, be treated with antitoxin. Aphthous vulvitis, due to infection with the fungus öidium albicans, does not appear to have been treated with vaccines, but since such excellent results have accrued in actinomycosis there would be, to my mind, every probability of such treatment being successful, were it worth one's while to make a vaccine for such cases, which it is not, since antisepsis is a sufficiently effective line of treatment.

Vaginitis.—Catarrhal vaginitis, if chronic, should certainly be treated with autogenous vaccines.

Granular vaginitis is usually due to gonorrhœa, and vaccines do much good in such subacute and chronic cases. Membranous vaginitis is diphtheritic or syphilitic. In the former case, antitoxin is, of course, indicated both for the local and general effects.

There is a curious form known as emphysematous vaginitis. Cysts containing gas (trimethylamin) are formed by short bacillary rods which are probably of the type of anaërobic gas forming bacilli in wounds. Eisenlohr (1) described this very rare form in 1888.

Gonorrhœa in Women.—This is the chief cause of ophthalmia neonatorum, and is therefore a highly relevant subject. Carriers of gonorrhœa are nearly always women. The gonococcus may lie dormant and the host unharmed, with evil sequelæ. The conscientious and persevering use of vaccines in such cases (as also in diphtheria carriers) will in time cure such carriers. The dosage is as for a case of arthritis, beginning with 25 millions and increasing gradually up to 1,000 millions on Haworth's lines. (Section I, Chapter IX.) Acute gonorrhœa is frequently followed by a mixed infection. Wertheim (2) reports 116 cases of pyosalpinx. Of these 72 showed no demonstrable germ in the pus (probably formerly specific), 32 showed the gonococcus, 6 showed the streptococcus, and 1 the staphylococcus. It is interesting to note that in 1897 Wassermann (3), who was working on the gonotoxin, found that filtrates of gonococcus cultures were non-toxic. Cultures produced local inflammation with fever, adenitis of the nearest glands, myalgia, and arthral-

gia. Here is a classical example, therefore, of a pure *endotoxin*. This also explains the therapeutic failure of gonococcal antitoxin, and confirms one's faith in vaccines for gonorrhœa. In women, the gonococcus is a deadly germ. To its account must be laid cases of vulvitis, Bartholinitis, vaginitis, inflammation of cervix and body of the uterus, salpingitis, ovaritis, and peritonitis.

Here is a great field for vaccine therapy. Systematic hunting of the gonococcus with vaccines has not yet become part and parcel of gynæcology, but it will, assuredly. Here at any rate specific therapy is not going to be a mere by-product or time-gainer. In the metastases of gonorrhœa, and in women, the knee is a favourite site ; vaccines are of great value. They may be used for diagnostic purposes also.

Urethritis — Cystitis — Infective Nephritis. — In treating any case of urethritis (refer to Section I, Chapter IX), especially in women, it should never be forgotten that tuberculosis may begin in the urethra. In the female, a chronic genital infection may lead to gonorrhœal cystitis or a septic cystitis. Bacillus coli cystitis is notoriously common in women, especially younger women. Vaccine treatment has been adequately dealt with in Section I, Chapter IX. Menstruation is the commonest time for a cystitis to begin in a woman. One remembers several cases where this held good.

In prescribing vaccines, the physician must take account of any possible calculi, displacements, neoplasms, cystocele, etc. A cystitis in the puer-

perium is generally very severe. Tuberculosis must invariably be watched for.

Endometritis.—Barbour (4) has pointed out that pure cultures of streptococci and staphylococci, if introduced into the healthy vagina, are destroyed in a few hours. The vaginal mucus is bactericidal, but in the puerperal state these *secretions are absent.* In the latter also, lacerations occur often, as also in intra-uterine operations or during removal of sloughing tumours. The organisms most commonly found are the—

Streptococcus pyogenes.
Staphylococcus aureus.
Various anaërobic seprophytes in sloughing tumours.
The gonococcus.
The tubercle bacillus.
The diphtheria bacillus. } Very rarely.
The spirochæte of syphilis. }

Acute Puerperal Endometritis.—This condition is usually streptococcal, occasionally gonococcal, and rarely due to other organisms. Bacteriological examination of an intra-uterine swab is essential. More often than not with the streptococcal type sapræmia yields to septicæmia.

In such a case the only thing the author knows to do good is a *fresh* polyvalent anti-streptococcal serum, 30 c.c. per diem to be given, intravenously at first, until marked improvement occurs, then by the subcutaneous route. The patient may take

weeks to improve in a bad case, but the experience I have had has been extremely encouraging. Vaccines in such cases are too toxic, even sensitized vaccines. In acute gonorrhœal endometritis, the prognosis is grave. A sensitized vaccine should be tried *faute de mieux*. The other varieties are dealt with in the usual manner.

Chronic Metritis and Pyometra.—Vaccines are useful. These conditions are often associated with a Bacillus coli infection from above.

Acute Oöphoritis.—The organisms concerned are:

The tubercle bacillus.
The gonococcus.
The streptococcus.
The staphylococci.
The Bacillus coli.
Anaërobic saprophytes. } Rarely.
Bacillus typhosus. } Rarely.
Pneumococcus. } Rarely.

The route of entry may be *via* the blood, *via* the lymphatics of the Fallopian tubes by spread of inflammation, as, for instance, from an inflamed appendix, malignant growth or suppurating wound. Severe puerperal infections and acute gonorrhœa account for some cases.

Where the organism can be utilized, vaccines apply to these cases as also to cases of chronic oöphoritis.

Recurrent abscesses of the Ovary must be treated on their merits.

Actinomycosis of the Ovary is very rare, but vaccines can be used with every hope of success.

Salpingitis (inflammation of the Fallopian tube). The tuberculous variety is common. An infected uterine cancer may cause it. Appendicitis may cause it by contagion. Puerperal sepsis may cause it by extension. Bacillus coli infection from the bowel may also cause it. A **tubo-ovarian** abscess may follow.

The germ often dies out. Alban Doran (5) has found an involutionary form of gonococcus in such cases.

Actinomycosis of the tube is not unknown. Where the causal germ can be certainly identified, vaccines can be used in all cases likely to do good. Where reinfection can occur of course vaccines are useless, and in any case they are never meant to supersede surgical and gynæcological technique and treatment. They are but adjuncts to such.

On the other hand, in pelvic **cellulitis,** pelvic **abscesses,** and in pelvic **peritonitis** vaccines are of great value, used discriminately.

In pelvic cellulitis, at a first operation it may be possible to identify the germ. Suppose it to be a gonococcus. Here a stock vaccine can be begun and an autogenous one prepared simultaneously. In tubercle, this does not apply. Sera and vaccines, so far, are useless in tubercle, but it may not always be so. In the case of septic germs, for instance, Bacillus coli or the pyogenic cocci, such as the staphylococci, autogenous vaccines should be used. In

the case of the streptococcus the serum should be used in the severest stages, then a sensitized vaccine.

In pelvic peritonitis, the same procedure should be adopted, except in the severest puerperal cases, when only a serum should be employed in the streptococcal variety. If adjacent appendicitis is the cause, vaccines are useless, naturally. In the gonorrhœal variety they must be used with caution, and it is safer to begin with small doses of a sensitized vaccine.

One has only been able to thus roughly map out the course of specific therapy in gynæcology, but by this time the author trusts the cardinal principles have become clear. Detailed treatment has been given in the first two sections of the book, and only exceptional conditions are dealt with more fully in this and the succeeding chapters.

CHAPTER II

NOTES ON SPECIAL DISEASES OF CHILDREN IN THE SAME CONNECTION

Infantile Diarrhœa.—In its most epidemic form, this very fatal disease is due to many different organisms. These are usually either—

Bacillus enteritidis sporogenes.
Streptococci and enterococci (see Glossary).
B. dysenteriæ (Shiga).
B. dysenteriæ (Flexner).

In the first instance, Wassermann demonstrated the utility of an anti-serum in horses. This is the rational treatment, but this field is largely unexplored. In the case of the other organisms, vaccines and sera should be employed. In children, oral administration is an easy way of giving them, *e.g.* in milk. The dosage is graduated accordingly. In urgent cases the rectal or subcutaneous routes are preferred, however.

Valvo-vaginitis of Children is usually gonococcal. A special technique is often necessary to demonstrate the cocci. Injecting a 1 in 2,000 solution of

bichloride of mercury in saline, followed by centrifugalization of washings, will often yield positive films, if not otherwise found. 5–10 millions of cocci every 5–7 days may be given subcutaneously.

Pertussis.—A hæmophilic bacillus (Bordet's bacillus) is the cause. In very severe cases 25 millions can be given to a child over 4 years of age. Prophylaxis with a stock vaccine is advisable in institutions or during epidemics. Three or four weekly doses of 5–10 millions each should be given. For curative purposes an autogenous strain is essential.

Pyrexia of Unknown Origin.—In children, pyrexia is easily caused. Naso-pharyngeal catarrh, latent otitis media, acute infective nephritis due to Bacillus coli, tonsilitis, diphtheria, hay-fever, and asthma also: bronchitis and broncho-pneumonia are cited by Still (1) as common causes.

Pneumococcal catarrh does very well with vaccines, non-pneumococcal catarrh fairly well. An initial minimal dosage is of course employed. Infective nephritis does very well also with an autogenous vaccine. Bronchitis and broncho-pneumonia, especially in prolonged cases, can be treated with vaccines. 5–10 millions can be given at one time to a child of 12 months every 4–5 days. In obtaining an autogenous specimen, it is well, as the author (2) pointed out, to excite cough and catch the sputum on a swab or platinum loop.

Still uses vaccines in **lobar pneumonia** in children. He advises 5–10 millions for a child of 6–9 months, or 10–15 millions for children of 1–5 years of age,

increased by 5 millions after four days. He is not, however, convinced of their efficacy. Nor is the author. Personally I expect much greater things from a pneumonic serum of the correct type. (See Part I, Chapter V, Section II.)

In **empyema,** the pneumococcus is commonly the organism present in children. Graham Forbes found that in 250 cases of children under the age of 12 that—

74·4%	had pneumococcal infections.
6·8%	had streptococcal infections.
18·8%	had mixed pneumococcal, streptococcal, and staphylococcal infections. One or two were infected with B. coli or B. proteus.
100.	

Still advises vaccines if the wound is unhealthy. I entirely agree. This worker has found tuberculin useless.

Tubercular Peritonitis.—Latham uses tuberculin per rectum. Still reports one cure.

Posterior Basic Meningitis and Cerebro-spinal Fever.—For ætiology and treatment see Section II, Chapter III.

Nephritis in Children (infective varieties).—This may be influenzal. It may also follow follicular tonsilitis or diphtheria or lobar pneumonia. An appropriate vaccine is invaluable in these cases, except in diphtheria, unless the Klebs-Lœffler germ is isolated from the urine, which is rare.

Pyelitis.—Coliform pyelitis is common. Pyelitis due to Bacillus proteus (G) is rare. Bowel or blood

infection may be the cause. If no pus is present, the infection is most likely indirect. Still gives autogenous vaccines thus:

To an infant 6 months old: 5 millions at first.
8–10 millions in 7 days.
15–20 millions after a week.

To a child of $3\frac{1}{2}$ years even 100 millions.

Epidemic Poliomyelitis.—See details in Section II, Chapter II, also Section IV.

Flexner and Clark found that urotropine lengthened the incubation period in this disease and may prevent paralysis. They gave 10 grains every 2 hours in severe cases, in an acidified urine.

Enuresis.—May be due to cystitis, and then can be relieved by an auto-vaccine.

Ophthalmia Neonatorum.—Is due to the gonococcus. Small doses of polyvalent stock vaccines, followed by an autogenous vaccine, are useful. Prophylactic stock vaccines are also useful.

Stomatitis.—May sometimes be treated with a vaccine if the organism is suitable.

The reader's attention is drawn to Section IV on auto-sera, especially in connection with such diseases as scarlet fever and poliomyelitis.

SECTION IV

MISCELLANEOUS

CHAPTER I

AUTO-SERUM THERAPY

THE serum of the same patient, or the serum of a recovering patient, may be removed and re-injected for therapeutic purposes, in certain diseases. As a last resort, it may be tried in obstinate skin troubles such as psoriasis, dermatitis herpetiformis, pemphigus, lichen planus and lichen ruber, urticaria and squamous eczema.

Bearing in mind the toxicology of the filterable virus (see Chapter II, Section II), it is not unexpected that in certain diseases it may be found possible to use the serum of a recovering patient to treat early acute and severe cases. Poliomyelitis has already been mentioned. Scarlet fever and small-pox furnish further instances. Reiss (1) noted marked improvement in the former following the intravenous injection of 50–100 c.c. of serum removed from two or more 3rd or 4th week convalescents. The serum is given as early as possible and is tested previously for—

(*a*) Sterility,
(*b*) Wassermann reaction.

It is removed under aseptic precautions, defibrinated with sterile glass beads, centrifugalized and preserved with phenol in suitable ampoules.

In severe and hæmorrhagic small-pox, Teissier (2) has reported good results.

In leprosy, the serum from cantharides blisters has been used with reported success.

Perhaps **salvarsanized auto-serum in parasyphilis** has been the most widely-used variety.

Salvarsan given intravenously in tabes dorsalis and general paralysis of the insane is ordinarily useless. This is because the choroid plexus prevents the passage of salvarsan, mercury, and antibodies. The same is true of anti-meningococcus serum and anti-tetanic serum, also of vaccine antibodies. The intraspinal injection of salvarsan is notoriously dangerous. Gibbs and Calthrop (3) got good results from the subcutaneous injection of serum from other patients who had received salvarsan.

Salvarsanized serum inhibits the spirochæte, more especially if heated to 56° C. for half an hour (4). Of course, early cases of parasyphilis are likely to benefit most. It must not be forgotten, however, that destroyed neurons cannot be replaced. In a large percentage of cases subjective symptoms have subsided and signs have become less marked, also the Wassermann reaction is modified.

The only untoward result the author has seen was spasmodic retention of urine lasting several months, requiring daily catheterization, which eventually became well in a tabetic.

Method of Administration.—0·6 or 0·9 gram of neosalvarsan or novarsenobillon is injected intravenously. One hour later, 40 c.c. of blood are withdrawn aseptically, allowed to coagulate, and centrifuged. Later, 12 c.c. of serum is pipetted off and diluted with 18 c.c. of sterile saline solution (0·85%). This 40% serum is heated at 56° C. for half an hour. After lumbar puncture, 25–30 c.c. of cerebro-spinal fluid are withdrawn. The serum is then injected, as with anti-tetanic serum, *very, very slowly*. Swift and Ellis find the gravitation method better. Later, 50–60% serum can be used, according to the reaction produced. The foot of the bed should be elevated.

Reaction.—This is usually mild. Slight temperature, some pain in the legs after a few hours is usually all. Kolmer (5) reports occasional maniacal symptoms, which he believes are due to the sudden liberation of the endotoxins of the killed spirochætes.

Examination of Cerebro-spinal Fluid.—There are three essential tests:

(1) The Wassermann reaction.
(2) The cell-count.
(3) The globulin test.

All these should be performed before treatment and after. Normally, 8 cells per cmm of fluid are

found. In parasyphilis, 50–100 per cmm., mostly small lymphocytes, are usual. A marked precipitate with the Noguchi-butyric acid test (G) is common.

Dosage.—A 7 to 21 days' interval is usual. If the Wassermann reaction, cell-count, and globulin test diminish in intensity, this is favourable. Aseptic meningitis (G) must be taken into account in reading cell counts.

Several, say 4–6 or even 10, repetitions are worth trying in improving cases.

This line of treatment is the only one with which we can at present improve the parasyphilitic or arrest this disease. Even so, we can do little enough, but this little may be very effective, and is well worth doing.

CHAPTER II

NORMAL SERUM THERAPY

Hæmorrhage.—The value of transfusion of the whole blood has been demonstrated during the war. Failing this, normal human, horse, or rabbit sera are of value, and of great value in some cases, in the treatment of hæmorrhagic toxicoses especially.

(1) Melæna neonatorum.
(2) Purpura hæmorrhagica.
(3) Hæmorrhagic retinitis.
(4) Intestinal bleeding in typhoid (but *not* vice surgery).
(5) Hæmorrhage of cirrhosis of the liver.
(6) ,, ,, pulmonary tubercle.
(7) Some cases of uterine hæmorrhage.
(8) Surgical operations on jaundice cases.
(9) Hæmophilia, especially where there is bleeding from the kidneys (Barringer (1)).

A case of a simple operation on the bladder in a hæmophiliac was followed by severe hæmorrhage. Cystotomy was performed and the bladder filled up with normal horse serum, after removing clots. Success was unequivocal (2).

This line of treatment is extremely simple, extremely little known, and little practised in this country (not so in America) and wonderfully effective. It should never be omitted in checking hæmorrhage in melæna neonatorum, hæmophilia, and post-operative hæmorrhage.

Infants and children require 10–20 c.c. Adults, 20–50 c.c. at a time. Anaphylaxis must be taken into account, naturally.

Precautions.—In transfusion of the whole blood, where time permits—

(*a*) A Wassermann test should be done.
(*b*) The donor's blood should be shown not to agglutinate or hæmolyse the recipient's red cells.

Serum in the Toxicoses of Pregnancy.—Injections of fresh serum (normal, of course) of pregnant women and horse serum are useful in the vomiting of pregnancy, possibly also in eclampsia, and in pruritus of pregnancy. Placental serum has been used also, illustrating the "hair of the dog that bit you" principle. The serum is, of course, to be duly tested beforehand.

Serum in Renal Conditions.—Teissier (3) assumes that the blood in the renal vein contains some of the internal secretions of the kidney, and uses such blood in nephritic conditions, especially in exacerbations of chronic nephritis and threatened anæmia. 10–50 c.c. per diem repeated for several days are given.

The experimental basis of such work requires further consolidation.

RÉSUMÉ

To fight the enemy with the best weapons in the world is the best way to beat him. To fight against disease is in no wise dissimilar in this respect. Nature's weapons are the best, and in specific therapy we are employing Nature's weapons. It is a cardinal principle that the nearer we get to Nature the more likely are we to succeed in these matters. Wherefore an autogenous vaccine is better than stock vaccine, and a serum of the right type, say in cerebro-spinal fever, is better than a polyvalent serum, for the same reason. The author now proposes to venture to classify to some extent vaccines and sera according to their therapeutic calibre. Every medical man is aware of the different calibres which these remedies possess. In diphtheria antitoxin we have a weapon of the heaviest calibre; with vaccines in septicæmia, we have a weapon of doubtful calibre, whose recoil is sometimes greater than we could wish. I propose therefore to adopt a provisional classification, based on personal experience.

Classification of Vaccines and Sera

(*a*) From the prophylactic point of view.
(*b*) From the curative standpoint.

Class I includes specific remedies of first-class importance: success is usual with these; failures are rare. Ordinary remedies are surpassed.

Class II includes specific remedies which are very valuable and which are becoming more effective as knowledge progresses. Failures are more frequent, however, than in Class I.

Class III includes specific remedies which accelerate a cure or achieve partial cure, but which require further elucidation. Failures at present are moderately frequent. Occasionally brilliant results accrue.

Class IV includes specific remedies of doubtful value. Some will give better results in the future; the majority will probably be discarded in course of time. Failures are frequent. Some of these are of the *faute de mieux* type, otherwise known as "time-gainers." Some, perhaps, are directly harmful, *e.g.* in septicæmia.

(*a*) Prophylactic Remedies

Class I:

Stock Vaccines:

Anti-cholera vaccine.
Anti-dysenteric vaccines (prepared after Graeme Gibson's method).
Anti-enterica vaccines.
Anti-furunculosis vaccines (local strains).
Anti-gonorrhœal vaccine (as regards complications).
Anti-pertussis vaccines.
Anti-plague vaccines.
Anti-rabic vaccine.
Anti-smallpox vaccine.
Vaccines to prevent "flares" and secondary hæmorrhage in chronic septic cases, especially gunshot wounds.

Sera :

Anti-tetanus serum.
Diphtheria antitoxin.

Immune serum in poliomyelitis.

Class II :

Anti-hay-fever vaccine.
Anti-influenza vaccine.
Anti-Malta-fever vaccine.

Class IV :

Anti-gangrene vaccine.
Anti-typhus vaccine.

(*b*) Therapeutic Remedies

Class I :

Autogenous vaccines :

Actinomycotic conditions.
Acute infective nephritis.
Cellulitis due to Bacillus pyocyaneus.
Cellulitis and whitlow generally.
Chronic gleet with secondary infections.
Chronic septic bronchitis with the Staphylococcus aureus as chief invader (complications of same, if any).
Furunculosis.
Hay fever.
Pneumococcal post-nasal catarrh.
Pyodermia.
Subacute typhoid cystitis.
Sycosis and impetigo.
Uncomplicated acute and subacute cystitis.

Sera :

Anti-streptococcal serum in puerperal sapræmia and septicæmia, if streptococcal.
Serum in hæmorrhagic toxicoses.
Serum in Type I pneumonia.
Serum in Type II pneumonia.

Class II :

Autogenous Vaccines :

Catarrhal asthma.
Chronic mixed-infection bronchitis.
Chronic empyemata.
Chronic endometritis and catarrhal infections of the female genital tract.
Chronic mastitis.
Conjunctivitis (infective).
Gonorrhœa generally and its complications.
Chronic septic gun-shot wounds (almost Class I).
Ludwig's angina.
Mixed post-gonorrhœal urethritis.
Non-pneumococcal post-nasal catarrh.
Pertussis.
Purulent bronchitis.
Vesicular eczema.
Local-strain vaccines generally.

Sera :

Anti-gangrene serum.
Anti-scorpion serum.
Anti-venin serum.
Immune serum in cerebro-spinal fever.
,, ,, in poliomyelitis.
,, ,, in Spirochætosis ictero-hæmorrhagica.
Serum in pregnancy toxicoses.

Class III :

Autogenous Vaccines :

Acne.
Chronic cystitis and chronic infective nephritis.
Chronic pelvic cellulitis of women
Chronic pelvic peritonitis of women
} Where the organism is identified.
Dysentery vaccines.
Vaccines in broncho-pneumonia.
,, in infective infantile diarrhœa.
,, in pyorrhœa alveolaris not due to B. Vincentii.
,, in typhoid fever.

Stock vaccines generally.

Sera :

Anti-plague serum.
Anti-streptococcal serum generally.
Anti-tetanic serum.
Immune serum in typhus fever.
Anti-dysentery sera.
Serum in Types III and IV pneumonia.

Class IV :

Anaërobic vaccines.
Anti-botulismus serum.
Coley's fluid.
Colitis, vaccines for.
Endocarditis, vaccines for.
Erysipelas, vaccines for.
Hypopyon ulcer, vaccines for.

Class IV (*continued*):

Chronic otitis media
Mycosis fungoides, etc.
Pneumonia
Rheumatoid arthritis
Septicæmia
Septic anæmias
} vaccines in.

Vaccines or sera in place of surgical or medical treatment.

As knowledge advances, this classification will have to be altered. As it lies, it depends upon a specific technique which has been described, combined with sound medicine, surgery, and gynæcology. Possibly few readers will thoroughly agree with it; possibly some will be pleasantly surprised. Nevertheless, it furnishes an answer of some kind to those who are trying to discredit and discourage specific therapy; and if it should be of any material use to those other sterling workers, the backbone of any hopeful line of treatment (and I refer to the general practitioners), then indeed the object with which this book was written will have been entirely consummated.

GLOSSARY

SECTION I

Chapter II

Opsonic Index is the ratio of the number of bacteria ingested by a given number of phagocytes in the presence of a patient's serum, to the number ingested by the same number of phagocytes in the presence of normal serum.

Chapter III

"Air-bacillus" (B. subtilis).—A sporing bacillus commonly found in straw. The commonest contamination of laboratory cultures.

Biuret Reaction or *Nin-hydrin* or *Piotrowski's Reaction* is performed thus: Treat 5 c.c. of a solution in which one suspects peptone (or albumose) with an excess of sodium hydrate and a drop of 1% solution of copper sulphate. A violet or pink colour indicates a positive result.

Chapter VI

Ætiology.—Causation.

Agglutination.—Certain germs, when treated with their specific anti-serum, in a short time lose their motility and adhere in clumps. Bacillus pyocyaneus (blue pus bacillus), if suspended in normal saline and warmed, soon agglutinates spontaneously. Agglutination is both a criterion of infection and a "reaction of immunity," *i.e.* part of the bodily defence against germs.

Agglutinins are antibodies that possess the power of causing bacteria, red blood cells, and some protozoa (trypanosomes) if suspended in a fluid to adhere and form clumps.

Atoxyl.—An arsenical compound used in the treatment of sleeping-sickness.

Autogenous Vaccine or *Auto-vaccine*.—A vaccine prepared from the patient's invading organisms.

Complement-deviation.—See chapter on Gonococcal Vaccines.

Endotoxin.—Intracellular poison contained within the bodies of bacteria and not liberated until their envelopes are broken up, *i.e.* not until they are dead: *e.g.* typhoid or gonorrhœa germs.

Exotoxin.—Extracellular poison excreted by the germs whilst alive, *e.g.* diphtheria.

Filterable Virus.—Fully explained in Section II, Chapter II.

Hæmolysis.—Solution of red blood cells. An opaque suspension of red cells in saline solution becomes clear upon hæmolysis occurring.

Staphylococcus aureus.—The growth on agar of this germ has a golden colour.

Staphylococcus citreus.—The growth on agar has a lemon colour at the edge particularly.

Staphylococcus albus.—The growth on agar is white. All three are Gram-retaining pyogenic cocci.

Trypanosomes.—Certain protozoa, the cause of sleeping-sickness.

Widal Reaction.—The agglutination reaction in typhoid fever (*vide infra*).

Chapter VII

Acne.—A chronic skin infection by the Staphylococcus albus and possibly other germs (so-called acne bacillus, a diphtheroid rod). "Blackheads," called comedones, and inflamed hair follicules are characteristic. Excessive secretion of sebum (seborrhœa), leading to plugging of the sebaceous ducts, usually starts the focus of infection.

Anaërobe.—A germ which as a rule cannot grow in the presence of oxygen. Many of this group form heat-resistant spores—for instance, B. Welchii, which, however, according to Kenneth Goadby, if grown in glucose-formate broth, refuses to spore consistently. Vaccines may therefore be admissible in this case, but the author considers them even so not devoid of risk.

Epiblast.—The embryonic superficial layer which yields the skin and its appendages and also the central nervous system.

Impetigo.—A septic inflammation of the skin accompanied by pustular crusts.

Indicanuria.—Excess of indican in the urine, an aromatic body whose presence therein points to intestinal toxæmia.

Mycosis fungoides.—A rare disease. Tumours of the skin occur, preceded by eczematous or urticarial patches. Probably it is the nature of a lymphosarcoma.

Pemphigus vegetans.—Also is rare. Bullæ appear first on the mouth, and then in moist situations such as the axillæ and groin. It may be fatal.

Pyodermia.—Superficial skin pustulation, primarily streptococcal.

Sycosis.—Septic folliculitis generally of the beard, often impetiginous.

Vesicular Eczema.—Watery vesicles appear on the hands and arms, succeeded by scaling and irritation, which latter generally spreads to the extensor surface of the forearms and legs, also occasionally to the chest, groin, abdomen, and feet. It is generally followed by boils containing the Staphylococcus citreus.

Vincent's Bacillus or *B. fusiformis.*—Curved rods and spirochætes; the two forms are found together. An anaërobe, it may cause severe ulcerative stomatitis with pyorrhœa or the latter alone. Vincent's angina refers to the former lesion.

Chapter VIII

Bacillus pyocyaneus.—A member of the coli-typhoid group which liberates green pigment and liquefies gelatine. Spontaneous agglutination is also one of its characters.

Ludwig's Angina.—Septic inflammation of the floor of the mouth, accompanied by adenitis and cellulitis, especially of the neck. It may be fatal.

Titre of Agglutination.—The highest dilution of a serum which will agglutinate a standard suspension of the germ to be tested constitutes the titre of agglutination.

Chapter IX

False Positive Reaction.—A serum which is contaminated with bacteria, especially if unheated, will deviate complement spontaneously: too strong an antigen will do the same thing. This yields an erroneous, in fact a false positive reaction.

Chapter X

Bacillus œdematiens (B. bellonensis var.).—One of the less common anaërobic wound-infecting organisms. It causes local œdema.

Bacillus of Malignant Œdema.—A sporing, Gram-negative rod, anaërobic in nature, and quite commonly a wound infector. In its virulent form the name is justified. The spores are central and oval.

Bacillus proteus.—One of the intestinal flora. It is not usually pathogenic, and liquefies gelatine like B. pyocyaneus. It has many varieties, as its name indicates.

Durham's Tube.—A small tube used inverted within a larger test-tube containing liquid media, *e.g.* 2% glucose in litmus-peptone water. Any gas

evolved through fermentation of the glucose collects inside the Durham's tube in so far as it is formed therein.

Chapter XII

Trench Fever.—A definite fever due to an intracorpuscular virus, possibly one of the filterable viruses (see Section II, Chapter II). Periostitis of the tibiæ and pyrexia are the commonest characters. It may be severe, and generally is relapsing.

Chapter XV

Tuberculin.—Preparations of the tubercle bacillus, in the nature of non-sensitized vaccines used therapeutically. There are numerous varieties.

SECTION II

Chapter II

"Street" Virus.—The virus from the brain or cord of a freshly killed rabid animal.

Chapter IV

High Potency Serum.—The serum of a horse which *happens* to yield a serum richer in antibodies than is usual. It may be a mixture of the richer sera.

Chapter VI

Thermostable Opsonin.—A heat-resistant antibody in the serum, which probably acts by making the bacteria more susceptible to destruction by the fluids of the blood and to assimilation by the phagocytes. It is most likely the potent factor in anti-anthrax serum, since heat up to 55° C. does not impair the latter's potency.

SECTION III

Chapter II

B. enteritidis sporogenes.—Discovered by Klein. A Gram-positive anaërobe, with terminal or subterminal spores. A gas-former. It causes fatal gas-gangrene in guinea-pigs, also some forms of summer diarrhœa.

The Enterococcus.—A short Gram-positive fæcal streptococcus. Not quite the same as St. fæcalis, since it ferments raffinose, which the latter does not. It is a facultative anaërobe, and is pathogenic to mice and rabbits.

SECTION IV

Chapter I

The Noguchi butyric acid test for globulin.

Technique (*Kolmer*).—In a test-tube place 0·2 c.c. of cerebro-spinal fluid, which must be clear. Add 1 c.c. of 10% butyric acid in normal saline. Heat and boil for a short time. Add 0·2 c.c. of normal sodium hydrate. Boil for a few seconds.

A granular precipitate appearing in a few minutes = a strongly positive reaction.

If no precipitate for one hour = a weakly positive reaction.

Slight opalescence after 2 hours = a negative reaction. 90% of G.P.I. cases give it and 60% of tabetics.

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